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Use of Nanotechnology in Agri-food Sectors and Apprehensions: An Overview

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ABSTRACT: The key challenge for the agriculture sector is to feed an ever-increasing global population with adoption of sustainable agricultural practices, integrating the goals of environmental health, economic profitability, and social equity. In this regard, nanotechnology is a globally rapidly growing ûeld of science and technology and casting an impact on every aspect of human life. It has also been recognized as one of its six “Key Enabling Technologies” by the European Commission, which contributes to sustainable competitiveness and growth in several industrial sectors. Considering the success of nanotechnology in different areas, application of nanoparticles (NPs) also started in agriculture but it is still in nascent phase. However, this could be a viable and sustainable option for instigating revolutionary changes in agricultural sector and the seed industry for delivering better outcomes in the coming years. Out of approx. 29000 patents on NPs granted worldwide, only 500 patents account for agriculture and nutrition aspects. Every year, several new nano-based agri-inputs and products are expected to be introduced into the market. Slowly but surely NPs are gaining attention of researchers, industry, end users and policy makers in India. The specific considerations for evaluation of NPs with a focus to address the issues regarding safe handling of nanofertilizers and nanopesticides (with or without nanocarriers) have been made in the recent guidelines from DBT in the context of Insecticide Act, Fertilizer Control Order, BIS and FSSAI. Hence, it would be interesting to use and carryout research on NPs, following new regulatory framework to be in place soon. Using nanomaterial as a carrier system for crop improvement and for enhancement of productivity would open new vistas for agriculture in the areas of pest/disease prevention, control and management, fertilizers, agrochemicals, biofertilizers and pheromones delivery, plant nutrients, anti-transpiration agents, plant growth regulators, biostimulants and plant genetic manipulation. Nanocarriers for nutraceutical delivery, nano processing aids, nanocomposites and nanosensors for safe applications in food, feed, packaging and dairy products would be gaining importance. NP based sensors could also have the potential to be employed as smart input delivery systems, determination of viability, losses, detection of seed borne pathogens in seeds and as growth monitoring, real time detection of pests, continuous monitoring of local environment etc. The results of nanoparticles used as seed priming agents to enhance seed germination, storage and crop productivity have been quite encouraging. Green synthesis protocols have gained extensive attention as a reliable, sustainable and eco-friendly means for the production of a wide range of nanomaterials. The researches on green NPs, their use in organic production and possibility of seed treatment applications have also been discussed in this. Since NPs are very infinitesimal in size and the quantity required for seed treatment purpose is still very less, it might not have an impact on flora and fauna above the threshold level. Still, the possible biosafety issues regarding use of NPs as seed treatment for improvement in seed germination, vigour and storability may arise. Considering the potential applications of NPs in many fields and the growing apprehensions of FDA about the toxic potential of nano products, it is need of the hour to look for new internationally agreed, unbiased toxicological models and focusing more on in vivo studies. Generally, science based evaluation of NPs and deliberations on the issues like; the possible ill effects of nano-particles on the environment, soil, plant nutrition and antagonistic effect on other nutrients, safety of workers, researchers, laboratory staff, seed industry and the health of general public, animals, insects and microbes etc. should only be the basis of policy decisions on NPs. The in-depth review of work done on mechanism and potential of nanoparticles in enhancing agricultural productivity and their possible impacts on ecosystem is also highlighted in this review.

Keywords: Agriculture and food, Nanobiosensors, Nanofertilizers, Nanotechnology and nanoparticles, Policy and regulations, Safety issues, Seed technology and treatments

The world is changing fast to meet the diverse demands of the rapidly increasing global population. The general awareness towards the health and environment is growing, and everyone is more concerned about the rampant exploitation of natural resources by the humans for their greed, which could be devastating for meeting the overall objective of food and nutritional security for future generations. The use of nanotechnology in agriculture has shown ray of hope to preserve the environment and provide avenues for sustainable agricultural development. Areas of physics such as nanoelectronics, nanomechanics, nanophotonics and nanoionics have evolved during the last few decades to provide a basic scientific foundation of nanotechnology. Nanoscience is the study of extremely small things and can be used across all the other science fields, such as chemistry, biology, physics, materials science, and engineering. Whereas, nanotechnology is application of science, engineering, and technology at the nanoscale, which is about 1 to 100 nanometers as per the definition used by the National Nanotechnology Initiative in the US. The lower limit is set by the size of atoms (hydrogen has the smallest atoms, which are approximately a quarter of an nm kinetic diameter), since nanotechnology must build its devices from atoms and molecules. The upper limit is more or less arbitrary but is around the size below which phenomena not observed in larger structures start to become apparent and can be made use of in the nano devices [1]. By comparison, typical carbon-carbon bond lengths, or the spacing between these atoms in a molecule, are in the range 0.12–0.15 nm, and a DNA double-helix has a diameter around 2 nm. On the other hand, the smallest cellular life-forms, the bacteria of the genus *Mycoplasma*, are around 200 nm in length. These new phenomena make nanotechnology distinct from devices, which are merely miniaturised versions of an equivalent macroscopic device; such devices are on a larger scale and come under the description of microtechnology [2]. The concept of the nanoworld is based on the convergence of a real mix of scientific and technological domains, which once were separate. This is a fabulous adventure where the frontiers between fundamental science and applied science become an area of exchange and innovation. If an object can be understood in detail at the microscopic level, we can use our knowledge to apply it to the macroscopic level too. In the beginning, there were only two dimensions in nanotechnologies. Specialists in optics then created almost perfect surfaces. The difficulty lay, and still lies, in how to deal with the third dimension; miniaturization race going from micro to sub-micro dimensions, all the while getting closer and closer to the nanometer. Furthermore, the concept of nano is becoming fashionable as it combines what we already know with new concepts and it conveys the idea of modern technology. An understanding of the basic concepts of quantum physics is of great importance as these laws rule the nanoworld.

The concept of bonding is as old as that of the atom. It's most famous interpretation came from the Greek philosopher Democritus, who saw that the bonding between atoms as a property linked to their shape, smoothness, and ability to lock onto other atoms. Chemical bonding can only really be explained with the knowledge of the quantum nature of the electron. Physicists talk about molecular orbitals, often represented in chemical formulae by a line, for example the C-C bond between two carbon atoms. This idea of a molecular orbital is very useful for visualizing the bonds between atoms. This is the most solid bond in chemistry, the universal adhesive which forms the basis of semi-conductor materials, such as molecules of living organisms. The evolution of nanoworld does not only concern electronics, since other fields of study such as mechanics, optics, chemistry and biology have also started creating their own nanoworld; commonly referred to as microsystems. Two main approaches are used in nanotechnology. In the “bottom-up” approach, materials and devices are built from molecular components, which assemble themselves chemically by principles of molecular recognition [3]. In the “top-down” approach, nano-objects are constructed from larger entities without atomic-level control [4]. Nanotechnology, in its original sense, refers to the projected ability to construct items from the bottom up, using techniques and tools being developed today to make complete, high performance products [5]. The duplication of millions of identical elements, as well as the links between them, admittedly leads to complications. The process of product development relies on the hierarchical organization defined in terms of components, machines and systems, which is almost similar to the organization seen in biological systems, where both self-growth and self- repair processes are complexly programmed. So, the complexity is also the part and parcel of the development process of cells and organisms and their multiplication.

The very idea of complexity is, in essence, multidisciplinary and is a notion that brings unpredictability into play. If biosystems are strongly hierarchical in terms of their levels, i.e. molecules, cells, organisms, and populations, then these four systems are interdependent, unlike computers. Complexity comes from unpredictable emerging functions in the bottom-up approach. These functions not only provide organisms with the sturdiness they need in order to live, but also create opportunities for evolutionary adaptation, depending on the external conditions. Nanotechnology is the engineering of functional systems at the molecular scale. Recently, the science of biology has become molecular and DNA, proteins, and cellular machinery etc. have turn out to be the subjects of multidisciplinary research areas. The investigations into these fields have been carried out by biologists, chemists, and physicists. It is well known that each protein has its own gene code, meaning that each gene determines the chain of a certain number of amino acids. This is only the beginning of understanding how molecular machinery functions. Furthermore, the tools that have been developed have created new areas of specialization, such as bioinformatics. The evolution of our know-how, and of technological innovations, had resulted in significant consequences. The internet is the fruit of the union between information technology and telecommunications, just as biochips are for electronics and biology. The imaging on a molecular level revolutionized the diagnostic techniques. The borders between chemistry, physics, mechanics and biology are disappearing with the emergence of new materials, such as intelligent systems, nanomachines, etc. The observation, image-processing and simulation have all benefitted from the advances in information technology and, conceptual progress and technical expertise is expected to go hand in hand in near future. This is where the nano tidal wave, which will have considerable impact on society, can be found.

Nanosciences and nanotechnologies are leading to a major turning point in our understanding of nature. Such a force has its consequences or in the words of a famous fictional character: every force has its dark side. Our future depends on how can we use new discoveries and what are the associated risks brought on humanity and our natural environment? Therefore, ethical implications of these technologies have to be taken into account. The nanomaterials (NMs) are of significant importance and increasingly being used for commercial purposes in various sectors, wherein some of the advanced NMs are at the forefront in biological and pharmaceutical sciences [6, 7]. However, nanotechnology applications in agriculture and food sector are relatively new and it is anticipated that advanced and designer nanomaterials will revolutionize agriculture and food sectors in the near future [8, 9]. Smart delivery of nutrients, bio-separation of proteins or other biomolecules, rapid sampling of biochemical contaminants and nano-encapsulation of nutraceuticals, plant protection / production, drug delivery systems for disease treatment, packaging materials for food security, development of new palates, textures and sensations, innovative materials for pathogen detection and delivery systems are some of the emerging research interests of nanotechnology for food and agriculture. Furthermore, advances in technologies, such as deoxyribonucleic acid (DNA) microarrays (DNA chip or biochip), agricultural water quality management, micro-electromechanical systems and micro fluidics, will enable the realization of the full potential of nanosciences for food applications [10, 11]. Likewise, production of agri-food products are of significant importance and it is the primary driving force of economy [12]. Moreover, recent research trends show that nanosciences have potential to advance agricultural productivity through genetic improvement of plants and animals, nano-array based gene-technologies for gene expression in plants and animals under stress conditions [13] and delivery of genes and drug molecules to specific sites at cellular levels in plants and animals [14]. The potential is increasing with suitable techniques and sensors being identified for precision agriculture [15], natural resource management, early detection of pathogens and contaminants in food products, smart delivery systems for agrochemicals like fertilizers and pesticides, smart systems integration for food processing, packaging and other interrelated areas like monitoring agricultural and food system security [16]. The innovative nano-intervention in agriculture and food sector could generate low-cost, high-efficacy solutions in terms of products and processes, especially suitable for developing countries. However, the unique properties can also lead to nanoparticle-related toxicity in humans and environment.

Although some studies showed the low toxic impact of nanomaterials in food and agriculture products [17, 18], the toxicity may be altered as a result from long-term exposure. It is better to take adequate precautions, as we know little about the bioavailability and biodistribution of nanomaterials therein and the ultimate acute and chronic toxicity upon exposure to them.

Recently, France has led the global trend to re-evaluate the safety of TiO_2 (E171) as food additives at the legislation level. In 2017, the French Agricultural Research Institute (INRA)-led research group reported the non-malicious, pre-tumorous damages in the colon of rats fed with TiO_2 NPs over 100 days of treatment [19]. Later, the French Food safety agency (ANSES) evaluated the French INRA study and made recommendations on the carcinogen potential of TiO_2 to European Chemicals Agency (ECHA). During mid-2018, one of the French Farm and Food bill amendments that passed the National Assembly, yet not final, is targeted to ban on the import and marketing of TiO_2 additives in food products by 2020 [20]. Many French food manufacturers, like Mars Chocolat France, the French confectionery subsidiary of Mars Inc., have already announced to follow the ban on TiO_2. Similarly, Dunkin' Brands, a U.S. company, has also announced to remove the alleged TiO_2 NPs from Dunkin' Donuts' powdered sugar donuts. The progress regarding banning the use of E171 gives an example of how legislation would impact the application and marketing of nano-food products. Many other factors, such as public awareness and consumer acceptance, together with research progress and governmental legislations make the future of nanotechnology in food industry uncertain, in spite of all the exciting marketed applications.

The guidelines for evaluation of nanoproducts in agriculture and food are more challenging than the existing procedures for assessment of fertilizers or safety evaluation of pesticides or toxicity evaluation in food. The activity, efficacy and impact of nanomaterials (NMs) depend upon interaction of their physico-chemical parameters with diverse environmental factors and, therefore, require a multidisciplinary approach for development of new alternative strategies and methods for evaluation. There are no unanimously acceptable international guidelines for nano-agriproducts (NAPs). Various scientists/ stakeholders have felt the need to have specific guidelines for evaluation of products in various sectors of biological sciences developed through interventions of Nanotechnology. Though, a few provisions that are in place for nanomaterials include; Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), Environment Protection Act (EPA) of India also known as the Umbrella Act, Australian Pesticide and Veterinary Medicine Authority (APVMA), Organisation for Economic Co-operation and Development (OECD), and Food and Agricultural Organization/ World Health Organization (FAO/WHO) with certain specific guidelines for quality, safety and efficacy. However, new innovations with alteration of functionality of nanosystems make it difficult to apply a universal set of evaluation parameters for different nanoproducts with different applications. Many a times the case-by-case basis evaluation approach is advocated for NAPs. The multidisciplinary nature of nanotechnology and its rapidly increasing scope for development of commercially viable applications pose a huge challenge to regulatory bodies across the globe. Nanotechnology involves an amalgamation of knowledge from various disciplines of science, including chemistry, materials science, physics, biology, engineering and medicine. Such an interdisciplinary nature makes nanoscience an important domain to facilitate enhanced scientific and technological prospects and development of novel applications. Moreover, nanotechnology and nanoproducts are dealt by different ministries / departments, and thus convergence between the concerned agencies is also required. Therefore, it was imperative for the Government of India to modify the existing policies and also develop certain new standard guidelines for evaluation of novel products on the basis of current scientific understanding. Department of Biotechnology (DBT) was mandated to bring out manuals/ guidelines specifying procedures to facilitate the regulatory processes pertaining to development/ commercialization of nano products in India. The proposed guidelines are aimed at ensuring not only the quality and efficacy to encourage the commercialization of nanotechnology-based innovations but also safety of novel products by emphasizing high benefit to low risk ratio compared to bulk counterparts.

Because of the variety of potential applications (from industries to defence), governments have invested billions of dollars in nanotechnology research across the world. As expected, these technological evolutions, not to speak of revolutions, bring with them some concerns since change does not come naturally to humanity and societies. We must, therefore, be aware about the ongoing challenges and what's at stake in the process. *De novo* nanomaterials (NMs) are being developed that provide us with application opportunities in sorted manner. However, increased usage of nanoparticles (NPs) may pose challenge to safety issues for the environment and warrant limited human activity. In fact, all scientific disciplines, including every single sector (such as nanomaterials, micro and nanomachines, micro and nanoelectronics), have their own paradigm. Hence, innovations and industrial developments are profoundly different. However, these fields are strongly interlinked. It is therefore necessary to focus on more interdisciplinary studies in order to enable us to understand the nanoworld. A comprehensive public debate may be required so as to address the tangible or possible risks and their bona fide consequences. Will humanity be able to master these new applications or are we taking on an unfamiliar role? We need to discover world of NPs in all its varieties, specifically in relation to agriculture. This article is a compilation of available information to take through the journey to territory of magical nanoparticles, the world of the small and the smallest parts, of micro and nanotechnologies.

Historical Perspective

The 4th century Lycurgus cup represents one of the outstanding achievements of the ancient glass industry and this cut glass vessel is extraordinary in several respects. Firstly, in the method of fabrication and the exceptional workmanship involved and secondly in terms of the unusual optical effects displayed by the glass. The glass trophy bears a scene involving King Lycurgus of Thrace, appears jade green when lit from the front but blood-red when lit from behind—a property that puzzled scientists for decades after the museum acquired the cup in the 1950s. The mystery wasn't solved until 1990, when British researchers scrutinized broken fragments under a microscope and discovered that the Roman artisans were nanotechnology pioneers: They had impregnated the glass with particles of silver and gold, ground down until they were as small as 50 nanometers in diameter, less than one-thousandth the size of a grain of table salt. However, the ancient Greeks imagined the atom as the smallest unit, which could not be split.

No one imagined that the colourful secret of a 1,600-year-old Roman chalice at the British Museum holds the key to super-sensitive and useful new technologies that might pinpoint biohazards at security checkpoints or help diagnose human diseases or could revolutionize the industries or be the game changer in agriculture. The ideas and concepts behind nanoscience and nanotechnology started with a talk entitled "There's Plenty of Room at the Bottom" by physicist Richard Feynman [21] at an American Physical Society meeting at the California Institute of Technology (CalTech) on December 29, 1959, long before the term nanotechnology was used. In his talk, Feynman described a process through which scientists would be able to manipulate and control individual atoms and molecules. Later Professor Norio Taniguchi [22] coined the term "nanotechnology" in his explorations of ultra precision machining during 1974. However, it wasn't until 1981, with the development of the scanning tunnelling microscope that could "see" individual atoms and modern nanotechnology began. Some of the important events in the history of nanotechnology [23] have been mentioned in table 1.

What are Nanomaterials?

Several phenomena become pronounced as the size of the system decreases. These include statistical mechanical effects, as well as quantum mechanical effects, for example the "quantum size effect" where the electronic properties of solids are altered with great reduction in particle size. This effect does not come into play by going from macro to micro dimensions. However, quantum effects can become significant when the nanometer size range is reached, typically at distances of 100 nanometers or less, the so-called quantum realm. Additionally, a number of physical (mechanical, electrical, optical, etc.) properties change as compared to macroscopic systems. One example is the increase in surface area to volume ratio; altering mechanical, thermal and catalytic properties of materials. Diffusion and reactions at nanoscale, nanostructures materials and nanodevices with fast ion transport are generally referred to nanoionics. *Mechanical* properties of nanosystems are of interest in the nanomechanics research. The catalytic activity of nanomaterials also opens potential risks in their interaction with biomaterials. Materials reduced to the nanoscale can show different properties compared to what they exhibit on a macroscale, enabling unique applications. For instance, opaque substances can become transparent (copper); stable materials can turn combustible (aluminium); insoluble materials may become soluble (gold). A material such as gold, which is chemically inert at normal scales, can serve as a potent chemical catalyst at nanoscales. Much of the fascination with nanotechnology stems from these quantum and surface phenomena that different organisms and molecules/biomolecules exhibit at the nanoscale [56] as listed in table 2.

Modern synthetic chemistry has reached the point where it is possible to prepare small molecules to almost any

Table 1. Important events in the history of nanotechnology

Date	:	Description
4th Century (AD)	:	The Lycurgus cup (Rome) is an example of dichroic glass; colloidal gold and silver in the glass
6th-15th Centuries	:	Vibrant stained glass windows in European cathedrals owed their rich colours to nanoparticles of gold chloride and other metal oxides and chlorides; gold nanoparticles also acted as photocatalytic air purifiers.
9th-17th Centuries	:	Glowing, glittering ”luster” ceramic glazes used in the Islamic world, and later in Europe, contained silver or copper or other metallic nanoparticles.
13th-18th Centuries	:	“Damascus” saber blades contained carbon nanotubes and cementite nanowires - an ultrahigh-carbon steel formulation that gave them strength, resilience, the ability to hold a keen edge, and a visible moiré pattern in the steel that give the blades their name.
1857	:	Michael Faraday [24] discovered colloidal “ruby” gold, demonstrating that nanostructured gold produces different-colored solutions under certain lighting conditions.
1908	:	Light scattering nanoparticles [25].
1928	:	Near-field optical microscope for for extending microscopic resolution into the ultra-microscopic region [26].
1932	:	Invention of TEM; transmission electron microscope [27].
1936	:	Erwin Müller [28], working at Siemens Research Laboratory, invented the field emission microscope, allowing near-atomic-resolution images of materials.
1947	:	John Bardeen, William Shockley, and Walter Brattain at Bell Labs discovered the semiconductor transistor and greatly expanded scientific knowledge of semiconductor interfaces, laying the foundation for electronic devices and the information age.
1950	:	Victor La Mer and Robert Dinegar developed the theory and a process for growing monodisperse colloidal materials - Controlled ability to fabricate colloids enables myriad industrial uses such as specialized papers, paints, and thin films, even dialysis treatments.
1951	:	Erwin Müller [29] pioneered the field ion microscope, a means to image the arrangement of atoms at the surface of a sharp metal tip; he first imaged tungsten atoms.
1953	:	Discovery of DNA [30].
1956	:	Arthur von Hippel at MIT introduced many concepts of—and coined the term—”molecular engineering” as applied to dielectrics, ferroelectrics, and piezoelectrics
1958	:	Jack Kilby of Texas Instruments originated the concept of, designed and built the first integrated circuit, for which he received the Nobel Prize in 2000.
1959	:	Richard Feynman of the California Institute of Technology gave what is considered to be the first lecture on technology and engineering at the atomic scale, “There’s Plenty of Room at the Bottom” at an American Physical Society meeting at Caltech [21].
1964	:	Zeolites and catalysis; catalytic cracking of hydrocarbons with a crystalline zeolite [31].
1965	:	Invention of ferrofluids; low viscosity magnetic fluid was obtained by the colloidal suspension of magnetic particles [32].
1965	:	Intel co-founder Gordon Moore described several trends he foresaw in the field of electronics in ”Electronics” magazine. One trend now known as “Moore’s Law,” described the density of transistors on an integrated chip (IC) doubling every 12 months (later amended to every 2 years). Moore also saw chip sizes and costs shrinking with their growing functionality-with a transformational effect on the ways people live and work. The basic trend Moore envisioned has continued for last 50 years is to a large extent due to the semiconductor industry’s increasing reliance on nanotechnology, as ICs and transistors have approached atomic dimensions.
1970	:	Predicted the existence of C60 in the form of icosahedrons [33].
1974	:	Tokyo Science University, Professor Norio Taniguchi coined the term nanotechnology to describe precision machining of materials to within atomic-scale dimensional tolerances [22].
	:	Molecular electronics; Application of molecular building blocks for the fabrication of electronic components using nanotechnology [34].
1977	:	Discovery of Surface Enhanced Raman Spectroscopy (SERS) [35].
1980	:	Discovery of Self-Assembly Monolayers (SAMs) [36].
1981	:	Gerd Binnig and Heinrich Rohrer at IBM’s Zurich lab invented the scanning tunnelling microscope, allowing scientists to “see” (create direct spatial images of) individual atoms for the first time. Binnig and Rohrer won the Nobel Prize for this discovery in 1986.
	:	Russia’s Alexei Ekimov discovered nanocrystalline, semiconducting quantum dots in a glass matrix and conducted pioneering studies on their electronic and optical properties.
	:	An approach to the development of general capabilities for molecular manipulation through Molecular Engineering [37].
1982	:	Development of the concept of DNA Nanotechnology [38].
1983	:	Discovery of colloidal Quantum Dots [39].

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Date	Description
1985	Rice University researchers; Harold Kroto, Sean O'Brien, Robert Curl and Richard Smalley discovered the Buckminsterfullerene (C60), more commonly known as the buck ball, which is a molecule resembling a soccer ball in shape and composed entirely of carbon, as are graphite and diamond. The team was awarded the 1996 Nobel Prize in Chemistry for their roles in this discovery and more generally that of the fullerene class of molecules.
	Bell Labs' Louis Brus discovered colloidal semiconductor nanocrystals (quantum dots), for which he shared the 2008 Kavli Prize in Nanotechnology.
1986	Gerd Binnig, Calvin Quate, and Christoph Gerber invented the atomic force microscope, which has the capability to view, measure, and manipulate materials down to fractions of a nanometer in size, including measurement of various forces intrinsic to nanomaterials.
1989	Don Eigler and Erhard Schweizer at IBM's Almaden Research Center manipulated 35 individual xenon atoms to spell out the IBM logo. This demonstration of the ability to precisely manipulate atoms ushered in the applied use of nanotechnology
1990	Individual Xenon atoms arranged to form the letters IBM [40].
1990s	Early nanotechnology companies began to operate, e.g., Nanophase Technologies in 1989, Helix Energy Solutions Group in 1990, Zyvex in 1997, Nano-Tex in 1998 etc.
1991	Sumio Iijima of NEC is credited with discovering the carbon nanotube (CNT), although there were early observations of tubular carbon structures by others as well. Iijima shared the Kavli Prize in Nanoscience in 2008 for this as well as other advances in the field. CNTs, like buckyballs, are entirely composed of carbon, but in a tubular shape. They exhibit extraordinary properties in terms of strength, electrical and thermal conductivity, among others.
1992	C.T. Kresge and colleagues at Mobil Oil discovered the nanostructured catalytic materials, MCM-41 and MCM-48, now used heavily in refining crude oil as well as for drug delivery, water treatment, and other varied applications.
1993	Moungi Bawendi of MIT invented a method for controlled synthesis of nanocrystals (quantum dots), paving the way for applications ranging from computing to biology to high-efficiency photovoltaics and lighting. Within the next several years, work by other researchers such as Louis Brus and Chris Murray also contributed methods for synthesizing quantum dots.
1996	DNA-based method for rationally assembling nanoparticles into macroscopic materials; SAM of DNA + gold colloids [41].
1997	First nanotechnology company (Zyvex Technologies) founded.
1998	The Interagency Working Group on Nanotechnology (IWGN) was formed under the National Science and Technology Council to investigate the state-of-the-art in nanoscale science and technology and to forecast possible future developments. The IWGN's study and report, Nanotechnology Research Directions: Vision for the Next Decade (1999) defined the vision for and led directly to formation of the U.S. National Nanotechnology Initiative in 2000.
	Creation of a Transistor using carbon nanotubes [42].
1999	Cornell University researchers; Wilson Ho and Hyojune Lee probed the secrets of chemical bonding by assembling a molecule [iron carbonyl Fe (CO) 2] from constituent components [iron (Fe) and carbon monoxide (CO)] with a scanning tunnelling microscope.
	Chad Mirkin at Northwestern University invented dip-pen nanolithography® (DPN®), leading to manufacturable, reproducible "writing" of electronic circuits as well as patterning of biomaterials for cell biology research, nanoencryption, and other applications.
1999–early 2000's	Consumer products making use of nanotechnology began appearing in the marketplace, including lightweight nanotechnology-enabled automobile bumpers that resist denting and scratching, golf balls that fly straighter, tennis rackets that are stiffer (therefore, the ball rebounds faster), baseball bats with better flex and "kick," nano-silver antibacterial socks, clear sunscreens, wrinkle- and stain-resistant clothing, deep-penetrating therapeutic cosmetics, scratch-resistant glass coatings, faster-recharging batteries for cordless electric tools, and improved displays for televisions, cell phones, and digital cameras.
2000	The National Nanotechnology Initiative (NNI) was launched to coordinate federal R&D efforts and promote U.S. competitiveness in nanotechnology.
2001	Molecular nanomachines: molecular motor (rotor) with nanoscale silicon devices [43].
2002	Carbon nanotubes functionalized with DNA [44].
2003	US enacted the 21st Century Nanotechnology Research and Development Act (P.L. 108-153). The act provided a statutory foundation for the NNI, established programs, assigned agency responsibilities, authorized funding levels, and promoted research to address key issues.
2003	Naomi Halas, Jennifer West, Rebekah Drezek, and Renata Pasqualin at Rice University developed gold nanoshells, which when "tuned" in size to absorb near-infrared light, serve as a platform for the integrated discovery, diagnosis, and treatment of breast cancer without invasive biopsies, surgery, or systemically destructive radiation or chemotherapy.

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Date	:	Description
2004	:	The European Commission adopted the Communication "Towards a European Strategy for Nanotechnology," COM(2004) 338, which proposed institutionalizing European nanoscience and nanotechnology R&D efforts within an integrated and responsible strategy, and spurred European action plans and ongoing funding for nanotechnology R&D.
	:	Britain's Royal Society and the Royal Academy of Engineering published Nanoscience and Nanotechnologies: Opportunities and Uncertainties advocating the need to address potential health, environmental, social, ethical, and regulatory issues associated with nanotechnology.
	:	SUNY Albany launched the first college-level education program in nanotechnology in the United States, the College of Nanoscale Science and Engineering
	:	Discovery of grapheme [45].
	:	Discovery of fluorescent carbon dots [46].
2005	:	Erik Winfree and Paul Rothemund (California Institute of Technology) developed theories for DNA-based computation and "algorithmic self-assembly" in which computations are embedded in the process of nanocrystal growth.
	:	Nanocar with turning buckyball wheels [47]. James Tour and colleagues at Rice University built a nanoscale car made of oligo (phenylene ethynylene) with alkynyl axles and four spherical C60 fullerene (buckyball) wheels. In response to increase in temperature, the nanocar moved about on a gold surface as a result of the buckyball wheels turning, as in a conventional car. At temperatures above 300°C, it moved around too fast for the chemists to keep track of it!
2006	:	DNA origami [48].
2007	:	Angela Belcher and colleagues at MIT built a lithium-ion battery with a common type of virus that is non-harmful to humans, using a low-cost and environmentally benign process. The batteries have the same energy capacity and power performance as state-of-the-art rechargeable batteries being considered to power plug-in hybrid cars, and they could also be used to power personal electronic devices.
2008	:	The first official NNI Strategy for Nanotechnology-Related Environmental, Health, and Safety (EHS) Research was published, based on a two-year process of NNI-sponsored investigations and public dialogs. This strategy document was updated in 2011, following a series of workshops and public review.
2009	:	The discovery and development of the green fluorescent protein, GFP [49].
	:	Scanning tunnelling microscope (STM) describes the electronic and mechanical properties of individual molecules and the polymer chains [50].
2009–2010	:	Nadrian Seeman and colleagues at New York University developed several DNA-like robotic nanoscale assembly devices. One is a process for creating 3D DNA structures using synthetic sequences of DNA crystals that can be programmed to self-assemble using "sticky ends" and placement in a set order and orientation. Nanoelectronics could benefit: the flexibility and density that 3D nanoscale components allow could enable assembly of parts that are smaller, more complex, and more closely spaced. Another Seeman creation (with colleagues at China's Nanjing University) is a "DNA assembly line" and Seeman shared the Kavli Prize in Nanoscience for this work in 2010.
2010	:	Development of an ultra-fast lithography to create 3D nanoscale textured surface [51]. IBM used a silicon tip measuring only a few nanometers at its apex (similar to the tips used in atomic force microscopes) to chisel away material from a substrate to create a complete nanoscale 3D relief map of the world one-one-thousandth the size of a grain of salt-in 2 minutes and 23 seconds. This activity demonstrated a powerful patterning methodology for generating nanoscale patterns and structures as small as 15 nanometers at greatly reduced cost and complexity, opening up new prospects for fields such as electronics, optoelectronics, and medicine.
2011	:	The NSET Subcommittee updated the NNI Strategic Plan and the NNI Environmental, Health, and Safety Research Strategy, drawing on extensive inputs from public workshops and online dialog with stakeholders from Government, academia, NGOs, and the public, and others.
	:	TERI-Deakin Nano Biotechnology Centre was established by TERI's Sustainable Agriculture Division (earlier known as Biotechnology & Bioresources Division) in collaboration with Deakin University, Australia with the mandate of developing innovative nanobiotechnology-based solutions to address current challenges in the field of agriculture and environment.
2012	:	NNI launched two more Nanotechnology Signature Initiatives (NSIs) -Nanosensors and the Nanotechnology Knowledge Infrastructure (NKI), bringing the total to five NSIs.
	:	Artificial molecular machines: pH-triggered muscle-like [52].
2013	:	NNI starts the next round of Strategic Planning, starting with the Stakeholder Workshop.
	:	Stanford researchers develop the first carbon nanotube computer.
2014	:	NNI releases the updated 2014 Strategic Plan.
	:	NNI releases the 2014 Progress Review on the Coordinated Implementation of the NNI 2011 Environmental, Health, and Safety Research Strategy.
2016	:	Design and synthesis of molecular machines [53].
	:	Successfully detected the first direct evidence of gravitational waves, using the Laser Interferometer Gravitational-Wave Observatory (LIGO).
2018	:	World's smallest tic-tac-toe game board made with DNA [54].
	:	Shrinking objects to the nanoscale [55].
2019	:	DBT proposed draft guidelines for evaluation of nano-agri-input products and nano-agriproducts in India

Table 2. Size of different organisms and molecules/biomolecules on the micrometric and nanometric scale

Organisms and molecules/biomolecules	Size
Streptococcus	800 -10,000 nm
Escherichia coli	1,300 × 4,000 nm (width × length)
Poxvirus	230 × 320 nm (width × length)
Tobacco mosaic virus	15-300 nm
Poliomyelitis virus	27 nm
Influenza virus	85 nm
Bacteria	100 -1,000 nm
Red blood cells	7000 - 8000 nm
Phages T4	24 - 200 nm 200 × 80 - 100 nm (length × width)
Caudovirales – icosahedral phages	About 65 nm
Inoviridae – filamentous phages	About 4 - 6 nm
Micro Electro Mechanical (MEMS) devices	10 - 100 nm
Carbon nanotubes	1 - 3 nm diameter
Single-walled carbon nanotubes	1 - 2 nm
Multiwalled carbon nanotubes	2 - 25 nm
Milk fat globule diameter	0.1 - 100 ìm
Milk casein micelles	20 - 400 nm diameter
Milk lipoproteins	10 nm
Milk globular proteins	3 - 6 nm
Egg albumin	Mean size <100 nm
DNA molecule	About 2.5 nm wide
Haemoglobin	5.5 nm diameter
Myoglobin	3.5 nm diameter
Cytochrome c	3.1 nm diameter
Catalase	10.5 nm diameter
Ferritin	12.2 nm diameter
Virus	30 - 100 nm
Protein	5 - 50 nm
Microtubules	25 nm
Ribosomes	25 nm
Quantum dot (CdSe)	8 nm
Dendrimers	10 nm
Zein	200 nm
Nanosensors	<1000 nm
The peptidoglycan layer (cell wall) in Gram-positive bacteria	20 - 80 nm
The peptidoglycan layer (cell wall) in Gram-negative bacteria	2 - 7 nm + 7 - 8 nm outer membrane
Adenosine triphosphate synthase	10 nm
Cell membranes	About 10 nm
Simple molecules	1 - 10 nm
Sugar molecules	1 nm
Water molecules	About 0.3 nm
Hydrogen atom	0.1 nm
Atoms	0.1 - 1 nm

structure. These methods are used today to manufacture a wide variety of useful chemicals, such as pharmaceuticals or commercial polymers. This ability raises the question of extending this kind of control to the next-larger level, seeking methods to assemble these single molecules into supra-molecular assemblies consisting of many molecules arranged in a well-defined manner. These approaches utilize the concepts of molecular self-assembly and/or supra-molecular chemistry to automatically arrange themselves into some useful confirmation through a bottom-up approach. The concept of molecular recognition is especially important: molecules can be designed so that a specific configuration or arrangement is favoured due to non-covalent intermolecular forces. The Watson–Crick base pairing rules are a direct result of this, as is the specificity of an enzyme being targeted to a single substrate, or the specific folding of the protein itself. Thus, two or more components can be designed to be complementary and mutually attractive, so that they make a more complex and useful whole. Such bottom-up approaches should be capable of producing devices in parallel and be much cheaper than top-down methods, but could potentially be overwhelmed as the size and complexity of the desired assembly increases. Most useful structures require complex and thermodynamically unlikely arrangements of atoms. Nevertheless, there are many examples of self-assembly based on molecular recognition in biology, most notably Watson–Crick base pairing and enzyme-substrate interactions. The challenge for nanotechnology is whether these principles can be used to engineer new constructs in addition to natural ones?

Molecular nanotechnology, sometimes called molecular manufacturing, describes engineered nanosystems (nanoscale machines) operating on molecular scale. Molecular nanotechnology is especially associated with the molecular assembler, a machine that can produce a desired structure or device, atom-by-atom using the principles of mechanosynthesis. Manufacturing in the context of productive nanosystems is not related to, and should be clearly distinguished from the conventional technologies used to manufacture nanomaterials, such as carbon nanotubes and nanoparticles. When the term “nanotechnology” was independently coined and popularized by Eric Drexler (who at the time was unaware of an earlier usage by Norio Taniguchi), it referred to a future manufacturing technology based on molecular machine systems. The premise was that molecular scale biological analogies of traditional machine components demonstrated molecular machines were possible: by the countless examples found in biology, it is known that sophisticated, stochastically optimised biological machines can be produced. It is hoped that developments in nanotechnology will make possible their construction by some other means, perhaps using biomimetic principles. However, Phoenix [57] proposed that advanced nanotechnology, although perhaps initially implemented by biomimetic means, ultimately could be based on mechanical engineering principles, namely, a manufacturing technology based on the mechanical functionality of these components (such as gears, bearings, motors, and structural members) that would enable programmable, positional assembly to atomic specification [37]. The physics and engineering performance of exemplar designs were analyzed in Drexler’s book *Nanosystems*. In general, it is very difficult to assemble devices on the atomic scale, as one has to position atoms on other atoms of comparable size and stickiness. Another view put forth by Montemagno [58] is that future nanosystems will be hybrids of silicon technology and biological molecular machines. Richard Smalley argued that mechanosynthesis are impossible due to the difficulties in mechanically manipulating individual molecules. This led to an exchange of letters in the ACS publication Chemical & Engineering News, 2003 [59]. Though biology clearly demonstrates that molecular machine systems are possible, non-biological molecular machines are today only in their infancy. The leaders in research on non-biological molecular machines are Dr. Alex Zettl and his colleagues at Lawrence Berkeley Laboratories and UC Berkeley [60]. They had constructed at least three distinct molecular devices whose motion is controlled from the desktop with changing voltage: a nanotube nanomotor, a molecular actuator [61], and a nanoelectromechanical relaxation oscillator [62]. An experiment indicating that positional molecular assembly is possible, was performed by Ho and Lee at Cornell University in 1999. They used a scanning tunnelling microscope to move an individual carbon monoxide molecule (CO) to an individual iron atom (Fe) sitting on a flat silver crystal, and chemically bound the CO to the Fe, by applying a voltage.

The field of nanomaterials includes subfields which develop or study materials having unique properties arising from their nanoscale dimensions [63]. Interface and colloid science has given rise to many materials, which may be useful in nanotechnology, such as carbon nanotubes and other fullerenes, and various nanoparticles and nanorods. Nanomaterials with fast ion transport are related also to nanoionics and nanoelectronics. Nanoscale materials can also be used for bulk applications; most present commercial applications of nanotechnology are of this flavour. Huge progress has been made in using these materials for medical applications. Nanoscale materials such as nanopillars are sometimes used in solar cells, which combats the cost of traditional silicon solar cells. Development of applications incorporating semiconductor nanoparticles to be used in the next generation of products, such as display technology, lighting, solar cells and biological imaging. Recent application of nanomaterials include a range of biomedical applications, such as tissue engineering, drug delivery, and biosensors [64-67].

These seek to arrange smaller components into more complex assemblies. DNA nanotechnology utilizes the specificity of Watson–Crick base pairing to construct well-defined structures out of DNA and other nucleic acids. Approaches from the field of "classical" chemical synthesis (Inorganic and organic synthesis) also aim at designing molecules with well-defined shape e.g. bis-peptides [68]. More generally, molecular self-assembly seeks to use concepts of supramolecular chemistry, and molecular recognition in particular, to cause single-molecule components to automatically arrange themselves into some useful conformation. Atomic force microscope tips can be used as a nanoscale "write head" to deposit a chemical upon a surface in a desired pattern in a process called dip pen nanolithography. This technique fits into the larger subfield of nanolithography. Molecular Beam Epitaxy allows for bottom up assemblies of materials, most notably semiconductor materials commonly used in chip and computing applications, stacks, gating, and nanowire lasers.

These seek to create smaller devices by using larger ones to direct their assembly. Many technologies that descended from conventional solid-state silicon methods for fabricating microprocessors are now capable of creating features smaller than 100 nm, falling under the definition of nanotechnology. Giant magneto resistance-based hard drives already in the market fit this description, as do atomic layer deposition (ALD) techniques [69]. Peter Grünberg and Albert Fert received the Nobel Prize in Physics in 2007 for their discovery of Giant magnetoresistance and contributions to the field of spintronics. Solid-state techniques can also be used to create devices known as nanoelectromechanical systems or NEMS, which are related to micro-electro-mechanical systems or MEMS. Focused ion beams can directly remove material, or even deposit material when suitable precursor gases are applied at the same time. For example, this technique is used routinely to create sub-100 nm sections of material for analysis in Transmission electron microscopy. Atomic force microscope tips can be used as a nanoscale "write head" to deposit a resist, which is then followed by an etching process to remove material in a top-down method.

These seek to develop components of a desired functionality without regard to how they might be assembled. Magnetic assembly for the synthesis of anisotropic super paramagnetic materials such as recently presented magnetic nano chains [3]. Molecular scale electronics seeks to develop molecules with useful electronic properties. These could then be used as single-molecule components in a nanoelectronic device [70]. Synthetic chemical methods can also be used to create synthetic molecular motors, such as in a so-called nanocar.

Bionics or biomimicry seeks to apply biological methods and systems found in nature, to the study and design of engineering systems and modern technology. Biomineralization is one example of the systems studied. Bionanotechnology is the use of biomolecules for applications in nanotechnology, including use of viruses and lipid assemblies [71, 72]. Nanocellulose is a potential bulk-scale application.

These subfields seek to anticipate what inventions nanotechnology might yield, or attempt to propose an agenda along which inquiry might progress. These often take a big-picture view of nanotechnology, with more emphasis on its societal implications than the details of how such inventions could actually be created. Molecular nanotechnology is a proposed approach which involves manipulating single molecules in precisely controlled and deterministic ways. This is more theoretical than the other subfields, and many of its proposed techniques are beyond current capabilities. Nanorobotics centers on self-sufficient machines of some functionality operating at the nanoscale. There are hopes for applying nanorobots in medicine [73, 74]. Nevertheless, progress on innovative materials and methodologies have been demonstrated with some patents granted about new nanomanufacturing devices for future commercial applications, which also progressively helps in the development towards nanorobots with the use of embedded nanobioelectronics concepts [75, 76]. Productive nanosystems are "systems of nanosystems" which will be complex nanosystems that produce atomically precise parts for other nanosystems, not necessarily using novel nanoscale-emergent properties, but well-understood fundamentals of manufacturing. Because of the discrete (i.e. atomic) nature of matter and the possibility of exponential growth, this stage is seen as the basis of another industrial revolution. Mihail Roco, one of the architects of the USA's National Nanotechnology Initiative, has proposed four states of nanotechnology that seem to parallel the technical progress of the Industrial Revolution, progressing from passive nanostructures to active nanodevices to complex nanomachines and ultimately to productive nanosystems [77]. Programmable matter seeks to design materials whose properties can be easily, reversibly and externally controlled though a fusion of information science and materials science. Due to the popularity and media exposure of the term nanotechnology, the words picotechnology and femtotechnology have been coined in analogy to it, although these are only used rarely and informally.

Nanomaterials can dimensionally be classified in 0D, 1D, 2D and 3D nanomaterials. The dimensionalities play a major role in determining the characteristic of nanomaterials including physical, chemical and biological characteristics. With the decrease in dimensionality, an increase in surface-to-volume ratio is observed. This indicates that smaller dimensional nanomaterials have higher surface area compared to 3D nanomaterials. Recently, two dimensional (2D) nanomaterials are extensively investigated for electronic, biomedical, drug delivery and biosensor applications.

Tools and Techniques in Nanotechnology

There are several important modern developments in the field of nanotechnology. The atomic force microscope (AFM) and the scanning tunnelling microscope (STM) are two early versions of scanning probes that enabled the launch of nanotechnology. There are other types of scanning probe microscopy available as well. Although conceptually similar to the scanning confocal microscope developed by Marvin Minsky in 1961 [78] and the scanning acoustic microscope (SAM) developed by Calvin Quate and co-workers in the 1970s [79], newer scanning probe microscopes have much higher resolution, since they are not limited by the wavelength of sound or light. The tip of a scanning probe can also be used to manipulate nanostructures (a process called positional assembly). Feature oriented scanning methodology may be a promising way to implement these nano-manipulations in automatic mode [80, 81]. However, this is still a slow process because of low scanning velocity of the microscope.

Various techniques of nanolithography such as optical lithography, X-ray lithography, dip pen nanolithography, electron beam lithography or nano imprint lithography were also developed. Lithography is a top-down fabrication technique where a bulk material is reduced in size to nanoscale pattern. Another group of nanotechnological techniques include those used for fabrication of nanotubes and nano-wires, those used in semiconductor fabrication such as deep ultraviolet lithography, electron beam lithography, focused ion beam machining, nanoimprint lithography, atomic layer deposition, and molecular vapour deposition, and further including molecular self-assembly techniques, such as those employing di-block copolymers. The precursors of these techniques preceded the nanotech era, and are extensions in the development of scientific advancements, rather than techniques which were devised with the sole purpose of creating nanotechnology and results of nanotechnological research [82].

The top-down approach anticipates nanodevices that must be built piece by piece in stages, much as manufactured items are made. Scanning probe microscopy is an important technique both for characterization and synthesis of nanomaterials. Atomic force microscopes and scanning tunnelling microscopes can be used to look at surfaces and to move atoms around. By designing different tips for these microscopes, they can be used for carving out structures on surfaces and to help guide self-assembling structures. By using, for example, feature-oriented scanning approach, atoms or molecules can be moved around on a surface with scanning probe microscopy techniques [80, 81]. At present, mass production is expensive and time-consuming but very suitable for laboratory experimentation.

In contrast, bottom-up techniques build or grow larger structures, atom by atom or molecule by molecule. These techniques include chemical synthesis, self-assembly and positional assembly. Dual polarisation interferometer is one tool suitable for characterisation of self-assembled thin films. Another variation of the bottom-up approach is molecular beam epitaxy or MBE. Researchers at Bell Telephone Laboratories, like John R. Arthur, Alfred Y. Cho, and Art C. Gossard developed and implemented MBE as a research tool in the late 1960s and 1970s [83, 84]. Samples made by MBE were the key to discovery of the fractional quantum Hall effect for which the 1998 Nobel Prize in Physics was awarded.

MBE allows scientists to lay down atomically precise layers of atoms and, in the process, build up complex structures. Important for research on semiconductors, MBE is also widely used to make samples and devices for the newly emerging field of spintronics. However, new therapeutic products, based on responsive nanomaterials, such as the ultradeformable, stress-sensitive transfersome vesicles, are under development and already approved for human use in some countries [85].

Important Nanoparticles in the Agriculture and Food Sectors

Nanotechnology provides new agrochemical agents and new delivery mechanisms to improve crop productivity, and it promises to reduce pesticide use. With limited availability of nutrients and water resources, optimum agricultural growth can be achieved by improved crop production practices supported with effective use of modern technology. Nanotechnology is a novel and emerging approach that can be utilized in the agriculture sector for biotic and abiotic stress management, disease detection and nutrient absorption [86, 87]. It enhances the production and nutrient utilization efficiency of plants by consuming a small quantity of resources compared with conventional approaches. Nanoparticles (NPs) can boost plant metabolism because of their unique physiochemical properties, and hence, improve crop yield and nutritional value [88]. For instance, the application of copper NPs in watermelon improved plant growth and development compared with control [89]. Similarly, zeolites and hydrogels are reported to absorb environmental contaminants and improve soil water holding capacity [90].

Micronutrients such as Cu, Fe, B, Mn, Zn, Cl and Mo are being progressively depleted from the soil solution because of steady crop production. Chemical fertilizers have been used to solve this problem to obtain better plant growth but, due to leaching properties and deleterious environmental impacts, there is a need to minimize the nutrient losses in fertilization. Recently, the concept of nano-fertilizer has been gaining popularity because of its slow-release and minimum leaching properties. Chitosan NPs efficiently reduced fertilizer consumption and environmental pollution [86]. A combination of superabsorbent polymer with slow-release fertilizers significantly improved crop nutrition and yield by reducing ion and water loss [90]. Foliar or soil application of micronutrient nano-formulated fertilizers may be used to improve soil health with maximum nutrient uptake, that will ultimately improve plant growth. According to a report, application of CeO_2 and ZnO NPs did not enhance the macronutrient concentration in *Cucumis sativus* fruits. However, these NPs changed the fruit profile of micronutrients by obviously increasing their concentration in fruits [91]. Similarly, nano-materials such as multiwalled carbon nanotubes (MWCNTs) have been reported for their incredible ability to improve the growth of *Zea mays* by increasing water and micronutrient uptake efficiency [92]. Nano-titanium dioxide (TiO_2) application promoted chlorophyll synthesis and photosynthetic activity by increasing the ion uptake efficiency of spinach [93]. Considering this, nanotechnology may be used to enhance the B uptake and utilization efficiency of plants, resulting in reduced fertilizer requirements.

Nanomaterials play an important role regarding the fate, mobility and toxicity of soil pollutants and are essential part of different biotic and abiotic remediation strategies. Nanotechnology can boost agricultural production, and its applications include: 1) nanoformulations of agrochemicals for applying pesticides and fertilizers for crop improvement; 2) the application of nanosensors/nanobiosensors in crop protection for the identification of diseases and residues of agrochemicals; 3) nanodevices for the genetic manipulation of plants; 4) plant disease diagnostics; 5) animal health, breeding and poultry production; and 6) postharvest management. Precision farming techniques could be used to further improve crop yields, without damaging soil and water, reduce nitrogen loss due to leaching and emissions, as well. Nanotechnology uses include nanoparticle-mediated gene or DNA transfer in plants for the development of insect-resistant varieties, food processing and storage, nanofeed additives and increased product shelf life. The usages of some of the important nanoparticles in the agriculture and food sectors are mentioned in table 3.

Use of Nanotechnology in Food Sector

Food nanotechnology has infiltrated into many aspects of customer products, such as food packaging, additives, and food preservation. The recognition of this novel technology has advanced the food processing and storage in ensuring food safety. Many conventional chemicals added as food additives or packaging materials have also been found partially existing at nanometer

Table 3. Use of different nanoparticles by various sectors/industries

Metals/Oxides	:	Usage
Boron (B)	:	It plays a key role in a diverse range of plant functions, including cell wall formation and stability, maintenance of structural and functional integrity of biological membranes, movement of sugar or energy into growing parts of plants, and pollination, seed set and fruit quality [94]. The NPs are also used in insecticides, notably against ants, fleas, and cockroaches.
Calcium (Ca)	:	Calcium is a common constituent of multivitamin dietary supplements, but the composition of calcium complexes in supplements may affect its bioavailability, which varies by solubility of the salt involved. Increased the growth rate, affect the physiology of the plants and may help in the formulation of new nano growth promoters and nano-fertilizers for agricultural use [95].
Carbon (C)	:	Carbon nanoparticles (CNPs) because of their unique electric, optical, and chemical properties, as well as low toxicity and high biocompatibility, which makes it such a versatile nanomaterial particularly for the agricultural sector. CNPs are mainly used for the development of sensors and plant growth enhancers for improved crop productivity [96].
Clay ($Al_2O_3(SiO_2)_2(H_2O)_2$)	:	With the development of new techniques for chemical synthesis, it is possible to synthesize NMs not only with a symmetrical (spherical) shape but also having a variety of different nanoforms, such as nanoclays (polypropylene nanoclay systems) and nanoemulsions (lipophilic nanoemulsions), tubes, rods, disks, bars and sheets. The dsRNA of different plant viruses can be loaded on non-toxic, degradable, layered double hydroxide (LDH) clay nanosheets or BioClay. The dsRNAs and/or their RNA breakdown products provide protection against the Cauliflower Mosaic Virus (CMV) in sprayed tobacco leaves, but they also confer systemic protection to newly emerged, unsprayed leaves on viral challenge 20 days after a single spray treatment in tobacco [97]. Soil colloids and minerals, particularly clay and iron minerals, are considered as important sink for NMs. Nanostructured material such as clay minerals, hydroxyapatite, chitosan, polyacrylic acid, zeolite, etc. is used to develop fertilizers to be used for soil and/or foliar application. Large surface area of hydroxyapatite and its strong interactions with urea lead to slow release of N from urea [98].
Copper (Cu)	:	Copper nanoparticles (CuNPs) have attracted a great deal of attention from all over the world due to their broad-spectrum antimicrobial activity. Copper is one of the key micronutrients, which plays an important role in growth and development of plants. CuNP-based fertilizer and herbicide can be used in agriculture, besides used in healthcare and industry. However, there are growing concerns regarding the indiscriminate use of either copper or copper nanoparticles, which can cause toxic effects to plants and other living organisms [99].
Gold (Au)	:	Gold nanoparticles (GNPs) are of various shapes and sizes, synthesized using biomass and/or extract of the organism. Enzymes secreted by microorganisms and metabolites of plants act as reducing, stabilizing and capping agents for the production of these nanoparticles. The GNPs have antibacterial/antifungal properties that can be used to protect plants against pathogens [100]. In addition, they can be applied for pesticide identification and water purification. Nano-gold based immunosensor is effective to detect karnal bunt disease in wheat plants [101]. The colour of a gold nanoparticle solution and its maximum characteristic absorption wavelength will change with the particle size and inter-particle spacing. These properties are often used in the detection of hazardous chemicals, such as pesticide residues, heavy metals, banned additives and biotoxins in food [102].
Iron (Fe)	:	The formation of iron nanoparticles/nanocomplexes was reported as an ideal homeostasis mechanism evolved by plants to modulate uptake of desired levels of ionic iron [103]. The Fe_2O_3 NPs can replace traditional Fe fertilizers in the cultivation of plants [104].
Manganese (Mn)	:	Applying nano Mn as a foliar treatment could enable greater control on plant responses. However, exposure to nano-scale Mn in soil could affect plants in subtle ways, differing from bulk or ionic-Mn, suggesting caution in agriculture use [105].
Molybdenum (Mo)	:	The use of colloidal solutions of metals as micronutrients enhances plant resistance to unfavourable environmental conditions and ensures high yields of food crops due to the active penetration of nanoelements into the plant cells. The seed treatment with colloidal solution of Mo nanoparticles combined with microbial preparation can significantly stimulate nodule formation in plants [106].
Palladium (Pd)	:	Noble elements such as the gold/silver/palladium (Au/Ag/Pd) NPs are emerging as the most promising to design bioengineering materials that could to be employed as modern diagnostic tools and devices to combat serious diseases. Though, due to the cytotoxicity of Ag/Au/Pd NPs, there is need for further research to minimize the toxicity of these NPs. Palladium nanostructures are characterized by remarkable catalytic and optical properties and have been reported as prodrug activator, as photothermal agents and for anti-cancer/anti-microbial therapy [107].
Phosphorus (P)	:	NanoPfertilizer (Nano-KH_2PO_4) could promote higher physiological efficiency for P in both roots and shoots, which consequently induces higher biomass accumulation and also increase instant water use efficiency in plants [108].
Platinum (Pt)	:	Electrochemical sensors and biosensors based on novel nanomaterials such as carbon nanotubes (single and multi-walled), metallic nanoparticles (silver, gold, platinum, copper and zinc), and super paramagnetic nanoparticles are currently used in the detection of various toxins present in foodstuffs [109].

Contd...

Metals/Oxides	:	Usage
Potassium (K)	:	Potassium ions are an essential component of plant nutrition and NPs are found to enhance the availability of nutrients that are found in most soil types [110]. Potassium bromate ($KBrO_3$) is a strong oxidizer (E924) used to improve dough strength and rise height. Potassium bisulfite ($KHSO_3$) is used as a food preservative.
Silicon (Si)		SiNPs have distinctive physiological characteristics that allow them to enter plants and influence plant metabolic activities [111].
Silicon Dioxide (SiO_2)	:	Silica, either colloidal, precipitated, or pyrogenic fumed, is a common additive in food production. It is used primarily as a flow or anti-caking agent in powdered foods, such as spices and non-dairy coffee creamer, or powders to be formed into pharmaceutical tablets. It can adsorb water in hygroscopic applications [112].
Silver (Ag)	:	Medicinal use in antibacterials and antifungals in much the same way as larger silver particles [113].
Titanium Dioxide (TiO_2)	:	Titanium dioxide (TiO_2) applied via roots or leaves at low concentrations has been documented to improve crop performance through stimulating the activity of certain enzymes, enhancing chlorophyll content and photosynthesis, promoting nutrient uptake, strengthening stress tolerance and improving crop yield and quality [114].
Zinc (Zn) and Zinc Oxide (ZnO)	:	Zinc is an important component of various enzymes that are responsible for driving many metabolic reactions in all crops. If specific enzymes were not present in plant tissues, growth and development would have stopped Carbohydrate, protein, and chlorophyll formation is significantly reduced in zinc-deficient plants. Application of nano zinc to leaves after 14 days of seed germination increased the activity of three important enzymes within the plants: acid phosphatase, alkaline phosphatase and phytase. Zinc oxide nanoparticles are very much important due to their utilization in gas sensors, biosensors, cosmetics, drug-delivery systems, and so forth. Zinc oxide nanoparticles (ZnO NPs) also have remarkable optical, physical and antimicrobial properties and therefore, have great potential to enhance agriculture. The biogenic synthesis of ZnO NPs by using different plant extracts is also common nowadays. This green synthesis is quite safe and eco-friendly, compared to chemical synthesis [115].

scale. For example, food-grade TiO_2 NPs now have been found up to approximately 40% in the nanometer range [18, 116]. Although nanomaterials like TiO_2 NPs are generally recognized as low toxic under ambient conditions, long-term exposure to such nanomaterials may cause adverse damages [117]. The application of novel food nanotechnology, together with the presence of nanoscale chemicals has also attracted public attention regarding the potential risks. We carefully review current progress on the application of food nanotechnology in this section. Selected nanomaterials used in food products are listed in table 4. United State Food and Drug Administration (U.S. FDA) and European Commission (EC) are the main sources for legislation and regulation on food nanotechnology. Some authorizations made by the U.S. FDA and EC in table 4 are based on the risk assessment of the conventional particle size of a substance. Therefore, a case-by-case basis by the authority may be required for engineered NPs. A few applications under research and development (R&D) are also included in table 4 to indicate potential future applications.

Use of Nanotechnology in Agriculture Sector

In agriculture, nanotechnology is employed to increase food production, with equivalent or even higher nutritional value, quality and safety. Efficient use of fertilizers, pesticides, herbicides and plant growth factors/regulators are the most important means for enhancing crop production. Controlled release of pesticides, herbicides and plant growth regulators can be achieved *via* usage of nanocarriers. For instance, poly (epsilon-caprolactone) nanocapsules have been recently developed as herbicide carrier for atrazine [136]. The treatment of mustard plants (*Brassica juncea*) with atrazine loaded poly (epsilon-caprolactone) nanocapsules enhanced the herbicidal activity compared to commercial atrazine, showing a drastic decrease in net photosynthetic rates and stomatal conductance, a significant increase of oxidative stresses, and ultimately weight loss and growth reduction of tested plants [136]. Similarly, other nanocarriers like silica NPs [137] and polymeric NPs [138] have also been developed as modified release system to deliver pesticides in a controlled manner. Nanoscale carriers can be utilized to achieve the precise delivery and slow release. Such strategies are known as “precision farming” that improves crop yields but not damage soil and water [139]. Most importantly, use of nanoencapsulation can lower the dosage of herbicides, without any loss of efficiency, thus benefiting the environment positively. In addition to nanocarriers, nanoparticle-mediated gene or DNA transfer in plants have been used to develop insect-resistant varieties. More details can be found in previously published reviews [140, 141]. Moreover, certain nanomaterials per se can act as pesticides with enhanced toxicity and sensitivity. Metal oxide nanomaterials like

Table 4. Nanotechnology-enabled food products

Sector	Application	Nanomaterials (Manufacturer)	Current status	Note
Food processing	Colour additives	TiO_2	Exempt from certification	<1% by weight of the food [118].
		Synthetic iron oxide	Exempt from certification	<0.25% (for dogs and cats) and 0.1 (for human) % by weight of the finished food [118, 119].
	Additive or polymer production aid	ZnO Iron oxide Aluminium oxide Silicon dioxide Cobalt oxide Manganese oxide (E530)	Authorized by EC 10/2011	Authorization based on conventional particle size [120].
		Titanium nitride		No migration reported. Only to be used in PET bottles up to 20 mg/kg
		Carbon black	Authorized by EC 10/2011; no longer authorized by the U.S. FDA as additives	<2.5% w/w in the polymer
	Preservatives	Silver-silica(Nanox Intelligent Materials)	FCS Inventory[a]	FCN No. 1235. <4 ppm by weight of silver as an antimicrobial agent blended into polymers [121].
	Flavour carrier	Silicon dioxide (E551[d])	Authorized by EC 1334/2008	<10,000 mg/kg, excluding foods for infants and young children [122].
	Marking fruit and vegetables	Silicon dioxide (E551)	Exempt from certification	<2% of the ink solids [118].
	Anticaking agents	Silicon dioxide (E551)	REG[b]	<2% by weight of the food [123].
	Nutritional dietary supplement	Copper oxide Iron oxide		Approved for animal feed [121].
		ZnO	GRAS[c]	
Food contact packaging	Pesticide detection	Zinc Oxide QDs	R&D	[124]
	Pathogens detection	Magnetic nanosensors	R&D	[125, 126]
		Plasmonic nanosensors		[127]
		Fluorescent nanosensors		[128]
	Toxin detection	Fluorescent nanosensors	R&D	[125]
		Plasmonic nanosensors		[129]
		Phosphorescent QDs		[130]
	Edible film/coating	Chitosan/Nano-Silica Coating		Tested on Longan fruit [131].
		Poly-ε-caprolactone		Tested on fresh-cut “Red Delicious” apples [132].
		Nanoemulsion/Quinoa Protein/ Chitosan		Tested on fresh strawberries [133].
		Bio-nano-hybrid pectins and LDH-salicylate		Tested on fresh apricots [134].
		Nanoemulsion with lemongrass essential oil	R&D	Tested on fresh-cut *Fuji* apples [135].
	Flame Retardation	Bentonite ($Al_2O_34SiO_2nH_2O$)	GRAS	U.S. FDA 21CFR184.1155 [118].
	Additives, gas barrier, etc. Prevent abrasive wear	Montmorillonite (PolyOne Corporation Nanocor® Inc.)	FCS Inventory	FCN No.1163. [121].
		Montmorillonite Chromium (III) oxide (Toyo Seikan Kaisha Limited and Nanocor Incorporated)		FCN No. 932. [134].
		Nanoemulsion with lemongrass essential oil (Oerlikon Balzers Coating AG, Oerlikon Surface Solutions AG)		FCN No. 1839. For use at a thickness not to exceed 200 nm, not for use in contact with infant formula and human milk [135].

Sector	Application	Nanomaterials (Manufacturer)	Current status	Note
	Prevent abrasive wear	Titanium aluminum nitride (Balzers Aktiengesellschaft)	GRAS	FCN No. 302. The maximum thickness of the surface coating shall not exceed 5 μm [118].
	Heating enhancer in polyethylene terephthalate (PET) polymers	Tin antimony oxide (Nyacol Nano Technologies, Inc.)	FCS Inventory	FCN No. 1437. <0.05% by weight of the polymer [121].

a. FCS: Effective Food Contact Substance (FCS) notifications.

b. REG: Food additives for which a petition has been filed and a regulation issued.

c. GRAS: Generally Recognized as Safe.

d. E numbers are codes of specific substances used as food additives, approved by the European Food Safety Authority (EFSA).

ZnO, TiO_2, and CuO are widely studied to protect plant from pathogen infections, owing to their intrinsic toxicity, for example ZnO NPs. It has been demonstrated that ZnO NPs can effectively inhibit growth of microbes, such as *Fusarium graminearum* [142], *Aspergillus flavus*, *A. niger*, *A. fumigatus*, *F. culmorum* and *F. oxysporium* [143], exhibiting strong antifungal and antibacterial activity.

Conventional mineral fertilizers suffer substantially from low nutrient uptake as well as utilisation efficiencies and high losses. The development of nanofertilizers has presented a novel solution for such economic losses. Nanofertilizers are capable of reducing nutrient loss and enhancing nutrient incorporation by crops and soil micro-organisms [105]. Commercialized nanofertilizers are mainly the micronutrients at nanoscale (e.g., Mn, Cu, Fe, Zn, Mo, N, B etc.) as given in table 5. It is noted that the use of other nanomaterials (instead of the typical conventional crop fertilizers), such as carbon nano-onions [144] and chitosan NPs [145], canal so increase crop growth and quality. It is anticipated that the novel nanofertilizers will motivate and transform existing fertilizer production industries in the next decade.

Owing to many beneficial aspects of nanomaterials, nanosensors, particularly wireless nanosensors, have also been developed to monitor crop growth, nutrient efficiency, disease incidence and environmental conditions in field. Notably, engineered nanosensors can detect chemicals such as pesticides and herbicides, as well as pathogens in trace amounts with respect to food and agricultural systems. Such *in situ* and real-time monitoring system helps to remediate potential crop losses and improve crop production, together with the proper use of nanofertilizers, nanopesticides, and nanoherbicides. A recent report showed that copper doped montmorillonite can be used for on-line monitoring of Propineb fungicide in aquatic environments (both in fresh and salty water), with a low detection limit of about 1 μM [146]. Another study showed that nanomaterials like graphene can be developed to detect pathogen in wastewater [147] and purify it for use as drinking water [148], indicating potential application in aquaculture. Many other nanomaterials such as copper NPs [149], carbon nanotube [150], gold NPs [151] and silver NPs [152] have are being developed as nanosensors for real-time monitoring of environmental conditions and crop health and growth.

Use of nanoparticles and nanosensors for agricultural benefit are two completely different fields of research. Many biosensors are coated with particular proteins and work at nanoscale, but without any involvement of nanoparticles at the recognition level. On the other hand, biosensors can also use small particles (which can be termed as nanoparticles in true technical sense). A composite electrode coated with nanoparticles along with DNA or protein could be an example of such biosensors. Experts have reviewed the advancements in these separate fields elsewhere. These reviews are mostly specialized for areas like nanofertilizers [154], nanopesticides and plant protection [155], may be the nano vehicle-assisted nucleic acid or other cargo delivery, or nanosensors [156]. Nonetheless, research on nanoscale biology to enhance agricultural yields has taken a giant leap in the last two years. Therefore, there is a need to summarize these latest developments for a broader range of readers and an attempt has been made in this review to bridge these areas together with a special emphasis on the achievements of the past two years.

a. Smart agriculture

Smart agriculture is an agricultural management concept which uses modern technologies for the betterment of

Table 5. Nanotechnology-enabled agricultural products

Application	Commercial names	Manufacturer	Current status and legislation compliance	Nanomaterial compositions	Function of nanomaterials
Nanofertilizer	Nano-Ag Answer®	Urth Agriculture	Commercialized.	Unknown nanomaterials	#Fertilizer
	NanoPro™, NanoRise™, NanoGro™, NanoPhos™, NanoK™, NanoPack™, NanoStress™, NanoZn™.	Aqua-Yield® Operations, LLC	Commercialized. Compliance with OSHA HCS (29CFR 1910.1200) and WHMIS 2015 Regulations	Unknown nanomaterials	#Fertilizer
	pH5®	Bio Nano Technology, Giza, Egypt	Commercialized.	Unknown nanomaterials	#Increase permeability
	Saula Drip, Saula Solocross, Saula Motawazen		Commercialized.	Minor elements (Iron, Zinc, Manganese, Copper, Boron) NPs	#Fertilizer
	Ready to Use Spray, Plus (Concentrate)	Green Earth-Nano Plant, FL, USA	Commercialized. US patents (US 15/290,257, US 15/429,380)	Biohumus in size range 100–700 nm	#Fertilizer
	Nova Land-Nano	Land Green & Technology Co., Ltd., Taiwan	Commercialized.	Microelements as Mn, Cu, Fe, Zn, Mo, N NPs	#Fertilizer
Nanopesticides	N/A	N/A	R&D	Cu $(OH)_2$ NPs	Fungicide [153]
	N/A	N/A	R&D	Silica NPs	Controlled release [137]
	N/A	N/A	R&D	Polymeric NPs	Controlled release [138]
	N/A	N/A	R&D	ZnO NPs	Bactericide
	NANOCU®	Bio Nano Technology, Giza, Egypt	Commercialized.	Copper NPs bactericide	#Fungicide and
Nanoherbicides	N/A	N/A	R&D	Poly (epsilon-caprolactone) (PCL) nanocapsules	Controlled release [139]
Nanosensors	N/A	N/A	R&D	Copper doped montmorillonite	Propineb fungicide detection in aquatic environments [146]
	N/A	N/A	R&D	Graphene	Pathogen detection in wastewater [147]

The requisite information is as available on the company's website and authors cannot endorse its claims.

the quantity and quality of produce, without further environmental degradation. 'Smart' agricultural management does not involve further input of harmful chemicals in the form of fertilizers and pesticides, but rather achieving higher crop yield and quality by using next-generation technologies. Today, we have access to Internet, GPS, big data management, soil scanning and artificial intelligence. Use of these technologies in agricultural sector can improve productivity. Use of satellite images, drones, and GPS has facilitated real-time monitoring of crops and animals [157]. This will also lead to precise and reduced use of fertilizers and pesticides. Combined use of artificial intelligence, big data management, and a Smartphone app can help them determine a plant/animal health or pathogen attack without consulting an expert [158]. Biotechnological solutions can be made available in the near future where any farmer can determine the nutritional and microbiological status of a soil instantly. Most important of all, many of the above technologies do not require the presence of a farmer in his field all the time, thanks to the internet. Farmers using all these technologies simultaneously will be able to harvest the full potential of their agricultural land with less economic inputs. Conceptualized not more than a decade ago, smart farming has already become a reality in the developed countries. Since sensors, probes, slow release fertilizers and pesticides are key to 'smart', 'precise', and 'sustainable' agriculture, nanotechnology can contribute to this field with huge benefits.

b. Nanotechnology and nanobiosensors

Currently, the biggest challenges that concerns mankind are food security for a growing number of population, shrinkage of the cultivable areas, climate change and low productivity. All these concerns have engaged researchers in finding solutions using modern scientific technologies where the role of nanoscience and nanotechnology is beyond comparison [159]. Nanotechnology is the study of materials or structures between 1 and 100 nm sizes [160]. In this range, the materials offer unique size-dependent properties that differ significantly from the bulk material and can be physically explained by quantum effect. The nanomaterials also have increased surface to volume ratio; hence, a change in both physical property and chemical reactivity is found when compared to the bulk materials. These exceptional properties of materials can be used to develop systems or devices or another new material, which is not possible to achieve when made from bulk materials [161]. These excellent properties of the materials at the nano regime allow investigators to develop highly sensitive, fast, miniaturized sensory devices known as nanosensors. A nanostructured sensory system transducing a nanoscale biological event (reaction or binding) into a measurable output signal is known as nanobiosensor. A biosensor consists of three components. The first component is a recognition layer, which is formed by using enzymes, antibodies, cells, tissues, nucleic acids etc. The second layer is a transducer and the transduction unit can be electrochemical (electrical signal), optical (light intensity), piezoelectric (mass), magnetic (magnetic property), or calorimetric (heat). The third component is a detector that amplifies and converts the signal into a measurable output data, for instance a controller unit converting analog electrical data to a digital one [162].

The small size of nanostructures with special properties makes them ultrasensitive. It was envisaged that sensors of nanoscale might offer significant advantages over conventional sensors because of similarities to the detectable molecules, such as a single molecule or an atom. Another aspect of nanoscale device is the ultrafast response time, as the speed with which the species is detected depends on the sensor's dimension. Their small size, lightweight, and high surface to volume ratio make them ideal candidates for high signal amplification and trace amount detection [129]. All of these were initially thought to be unattainable.

c. Potential areas of exploitation in agriculture sector

Increasing crop productivity is of vital importance in agriculture because of the rapidly growing global population with diminishing resources as mentioned before. Few possible areas where nanotechnology can play its role are genetic improvement, yield increase, crop protection against insect-pests and diseases, and monitoring of crop health using nanosensors.

1. Use of nanoparticles in the genetic improvement of crops

Till date, gene delivery into plants relies on Agrobacterium infection or biolistic particle delivery. However, success in these methods is limited to few plant systems and is heavily genotype specific. The entry of DNA through the rigid cell wall and its stability before it can be replicated inside the cell are major roadblocks. Nanoparticles can overcome the cell wall barrier easily and can overcome the bottlenecks of current transgene delivery systems. Positively charged nanoparticles and nucleic acid conjugates can be directed into the plant cell. The DNA is protected from the enzymatic attack in the cytosol, but is released from the nanoparticles into the nucleus. The exact mechanism explaining the release and delivery of the transgene is not yet understood, but the implications are profound. A probable mechanism of enhanced transformation could be a change in zeta potential (in case of electroporation only). This has been shown by 'nanoplex' which is a complex of cell-penetrating amino acids (such as poly-lysine) and gold nanoparticles [163]. Nucleic acids conjugated with carbon nanotube scaffolds [164, 165] have been recently used in transgene integration. This has even overcome the species- or genotype-specific barriers, normally adopted in many gene delivery methods. Successful transformation in *Nicotiana benthamiana* (Tobacco), *Eruca sativa* (arugula), *Triticum aestivum* (wheat), and *Gossypium hirsutum* (cotton) by this method strengthens this fact [164]. Stable delivery of dsDNA has been the desired way to protect a plant from virus. However, a topical application of dsDNA to achieve plant defense was beyond our dream, due to the instability of naked DNA.

Double hydroxide clay nanosheets called 'BioClays' [97] have successfully protected a plant from virus over a period of a month. Similar work by Hajiahmadi, et al. [166] using modified mesoporous silica-coated dsDNA has shown significant result in the topical delivery of the CryIAb gene. DNA itself can be converted into solid stiff nanostructures, which can subsequently be used to carry other nucleotide cargo, like SiRNA [167]. Chloroplast transformation has been a dream for agricultural biotechnologists in recent years. The chloroplast genome is maternally inherited, which s prevents any transgene from chloroplast to be horizontally transferred to similar wild species through pollen. The rate-limiting step in this method is obviously chloroplast-specific transformation. Chitosan-complexed single-walled carbon nanotube has recently been used to achieve chloroplast-specific transformation of foreign genes in plants [168]. Elsewhere, use of nanoparticle–DNA conjugate in combination with magnetic field has been shown to construct stable transgenic plants [169] in a single step. This method called 'pollen magnetofection' directly produces a transgenic plant even without the need of tissue culture or regeneration, which are considered as the two major roadblocks in transgenic plant production. The two above-mentioned methods have the potential to revolutionize the technique for gene delivery into plants, and more such methods could be developed in coming years. These will definitely streamline the process of translation of the basic research, where successful plant transformation is a major bottleneck.

2. *Use of nanoparticles in improvement of seed planting value*

Rapid and uniform seedling emergence and early plant growth are the key determinants for realising potential crop yields. Seed has been regarded as the carrier of new technologies; however, potential of nanoscience has still remained untapped with respect to seed-based research, particularly in India. Nano-particulate systems have shown promise for increasing the biological activity and acting as delivery vehicle not only for PGR, but also for all pathological sufferings of plants as nanopesticides. Moreover, engineered nanoparticles (ENPs) have shown to enhance the seed germination and plant growth. The positive effect of is due to the capability of NPs to penetrate seed coat by creating new pores and therefore promote water uptake or by entering into the plant roots through osmotic pressure, capillary forces, pores on cell walls, and intercellular plasmodesmata or via the highly regulated symplastic route. All these systems can help to increase productivity indirectly when used for pest control, but few nanocarrier systems have been explored for application of plant growth regulators. Plant based materials seem to be the best candidates for synthesizing biocompatible NPs due to the biochemical diversity of plant extracts, non-toxic phytochemical constitutes, non-pathogenicity, low cost and flexibility in reaction parameters as compared to chemical synthesis methods. Natural polymers are usually biocompatible and biodegradable, thereby reducing the biosafety concerns.

Agriculture being a viable complex system has restricted the exponential growth of nanotechnology in the field of agriculture. Recently, functional nanoparticles are gradually gaining global attraction of agricultural scientists due to their infusion in seed invigoration, plant growth and pest control. In agriculture, nanoscience has initiated nanopriming5to improve germination of low vigour seeds. Application of nanoparticles with the mixture of nano-SiO_2 and nano-TiO_2 increased the nitrate reductase in soybean, thereby increasing its germination and growth [170]. Use of nanoparticles in rice germination elucidates significant reduction in root growth, increase in hydrogen peroxide levels and MDA content [171]. The chitosan nanoparticles were evaluated for its potential to inhibit the growth of phytopathogens in chickpea and it was evident from the results that chitosan nanoparticles inhibit the growth of phytopathogens tested and also showed positive morphological effects, such as enhanced germination per cent, seedling vigour index and vegetative biomass [172]. The effect of nanoparticles was also studied on the storability of KRH-4 hybrid rice seeds and it was found that Zinc oxide nanoparticles may be a feasible approach to increase the germination, vigour and storability [173].

As published [174] in Annual Report, 2018-19 of AICRP-NSP (Crops), nano particle seed treatments with zinc oxide@ 500 ppm recorded maximum values for seed quality parameters than control in pigeon pea, irrespective of varieties. The bulk formulation of zinc oxide@750 ppm also recorded similar results. But the effect was lesser than the nano treatments. During storage, silicon dioxide in nano form @ 100 ppm concentration recorded higher seed quality parameters germination (87%), mean seedling length (34.48cm), seedling dry weight (0.41 g), seedling vigour index I (3003) and vigour index II (3616) up to six months of storage period, followed by silicon dioxide @150 ppm as compared to other treatments. Based on the above results, it can be concluded that Nano formulations of Zinc oxide @ 500 ppm and Titanium oxide @250 ppm can be used effectively for enhancing the seed quality status of onion lots. Seed treatment with Titanium oxide nanoparticles@250 ppm recorded maximum values for all seed quality parameters than control, irrespective of varieties, whereas bulk formulation of 250 ppm Titanium oxide also recorded similar results, but the effect was lesser than the nano treatments.

The studies on soybean revealed non-significant differences with respect to germination percentage and seedling vigour indices among different concentrations for both nano and bulk form of all the nano-particles. However, significant differences were recorded among the nano formulations for field emergence percentage (out of twenty-five seeds each) in nano as well as bulk formulations with respect to electrical conductivity and nano formulations for dehydrogenase activity. The Electrical Conductivity (EC) reflects the damage to seed; and higher value of EC for control indicated low vigour of seed as compared to the treated ones and vice versa. Based on the result obtained from field emergence, electrical conductivity and dehydrogenase activity, it was observed that in case of variety Pusa 9712, nano and bulk formulations of silicon dioxide @ 500-750 ppm, followed by Titanium oxide @750 ppm and zinc oxide @ 1000ppm was found to be the most effective treatment. For variety Pusa 9814, nano and bulk formulations of silicon dioxide @ 750 ppm, followed by Zinc oxide @500 ppm and Titaniumoxide @ 1000ppm was found to be the most effective treatment for enhancing the seed quality.

Seed priming with silver nano conjugate-B + seedling root dip treatment before transplanting for 6 hours with B (1, 2, 4-triazolodithiocarbamate conjugated Silver nanoparticles aqua emulsions) and seed priming with silver nano conjugate-B resulted in maximum disease control and also gave maximum seed yield. As the results obtained from both these were statistically at par with each other, the need of seedling root dip for the management of seed borne inoculum of *Fusarium fujikoroi* may not be required.

The need of resilience to high temperatures under changing climate have posed a challenge to researchers for both, maintaining and achieving the high yields of agricultural commodities and particularly in the marginal crops cultivated under arid and semi-arid conditions. To address these challenges, a new technology is required which not only hastens the germination, but is also cost effective and can be performed by farmer himself [175]. Seed priming is a technique, where seeds are partially hydrated to resume the normal process of germination till radicle emergence [93]. Seed priming has been reported to improve seed quality, seedling establishment and crop yields as well as increasing tolerance to various biotic and abiotic stresses [176]. Further, applications of NPs on seeds have been reported to impart multiple benefits, like improved growth and resistance to biotic and abiotic stresses. Seed priming has been found to be useful for enhancing seed quality, seedling establishment and crop yields as well as increasing tolerance to environmental stresses [177]. Seed priming can improve the germination of weak, damaged or aged seeds or even under adverse environments [178]. A number of commonly used priming agents include polyethylene glycol, inorganic salts, nutrients, and plain water [179-181]. However, different priming solutions have different properties, effectiveness and optimization of priming agents is required for each crop species [180].

Till date, several experiments have been performed in order to define the effect of nano biomaterials on crop production. It has been well known that nanoparticles have positive morphological effects, like enhancement of seed germination rates, improvement of root and shoot formation and their ratio, as well as accumulation of vegetative biomass of seedlings in many crop plants. Nanoparticles influence at the cell level, thus increasing the pace of physiological processes in plants. In this regard, standardization of nano-based seed priming protocols, especially selection of priming agents, duration, temperature, osmoticum and storability potential will help in harnessing maximum benefits of this technology. Therefore, there is a growing need to develop new priming agents to enhance seed germination of various crop plants. Seed priming technology has been developed from a simple method involving soaking seed in predetermined amounts of water or limitation of the imbibition time. A vast scientific literature has been available on priming without using chemicals. However, nano priming of seeds in agriculture sector is still in experimental stage and doesn't seem to be well developed. The most commonly metal-based nanoparticles reported in recent years include AgNPs, AuNPs, CuNPs, FeNPs, FeS_2NPs, TiO_2NPs, ZnNPs, ZnONPs and carbon-based NPs ([93, 176, 181-188].

Nanotechnology has the potential to revolutionize the food and agricultural industries by enhancing crop productivity and quality [189]. Nanoparticles (NPs) can boost plant metabolism [190], enter into plant root and leaf cells, and carry chemicals into these cells [191] NPs cause many physiological and metabolic changes in plants, depending on the chemical composition, surface area, size, reactivity and dose of NPs used [192]. Seed germination and seedling emergence are critical factors that determine crop establishment and ultimately yield [177]. In nano priming, NP suspensions or emulsions NPs offer advantages over conventional priming methods.

Ironically, only a few researchers have used seed priming strategy, in which seeds must be redried to their original moisture content before sowing. Thus, the mechanism behind seed nano priming would be different from that of pre-sowing seed treatment without drying seeds. In addition, comprehensive studies on physiological and molecular mechanism of nano priming effects on seed germination have not been elucidated, and thus many questions still remain unaddressed, especially mechanism behind NPs-induced seed germination. There is a need to design and develop nano priming methodology that will be able to improve seed germination, reduce seed/soil borne pathogens and adequate nutrient availability at the time of seedling growth under poor soil conditions.

3. *Nanotechnology based fertilizers and seed biostimulants for rainfed agriculture*

In view of deteriorating soil health and water quality, uniquely poised path breaking technologies using biological interwoven with nanotechnologies and biocompatible materials are being developed. Different variants of nanofertilizer with better field performance having features like; scientifically developed products using nature expertise approach, containing efficiently stabilized essential nutrients in nanostructured form, higher use efficiency and slow release formulations tuned via the use of mesoporous nanocarrier systems are expected to be available soon. Graphene (2D nano carbon)-based seed biostimulant technology developed by TERI-Deakin Nanobiotechnology Centre (TDNBC) is stable and required in ultra-Small quantity (i.e. 10µg/g seed), gives consistent performance across crop and soil types, compatible with nanonutrients, herbicides, fungicides, and insecticides. Multifunctional nature as such provide protection from adverse effects of salts deposited on the seeds, especially in the rainfed/dryland areas where moisture evaporation is a very common phenomenon as well as from the soil-borne pathogens by making a physical barrier.

Recent development in nanotechnology has provided a wealth of diverse nanoscale carriers that can be applied to efficacious delivery of agri inputs [193]. Agri-input loading on surface or within the pores and matrix in the nanostructured materials have been recognized as a promising approach to enhance use efficiency and performance under diverse conditions [194-196]. Among them graphene is an emerging material that synergistically fuses nanotechnology and chemistry breakthroughs [197, 198]. The graphene synthesis and fabrication includes the reduction of graphene oxide into 2D generally single atom thick (1 nm) sheets to favour desirable nanomatrix with higher surface area with inherent plant biostimulant activity, along with value added biostimulant molecules loading and delivery [195, 199, 200]. The functionalized surface allows plant biostimulants the slow release in a specific manner, which can significantly increase seed viability, emergence and growth under dry land agriculture conditions, hence reducing the cost of the crop cultivation and increasing the agricultural productivity [199, 201]. Therefore, an attractive performance in respect of biostimulant, greater efficacy and smart delivery, graphene is a promising candidate for applications in agriculture [195, 199, 201].

The seed coat adsorption and penetration of graphene with immobilized biostimulant molecules might facilitate water uptake from soil particles, controlled release and smart delivery of biostimulant molecules, resulting in a viable and cost effective technique in comparison to conventional methods. The graphene based biostimulant formulation mediated approach may have several advantages over other products, e.g. (i) loading of higher amounts of biostimulant molecules per unit area of graphene, (ii) highly efficacious in nature via slow release and smart delivery nature, (iv) higher stability and water sequestration property under dry land agriculture conditions. However, other carbon NMs mediated delivery of biostimulants have challenges such as (i) poor stability, (ii) lower efficacy due to the bulk nature or less surface area (iii) presence of impurities of toxic metals and radioactive elements and (iv) toxicity and (v) lack of smart delivery i.e. very difficult to allow surface modification and functionalization. Thus, graphene based innovative biostimulant nanoformulations may have additional technological and economic advantages for the industrial production of highly efficacious innovative product for increasing the productivity of dry land agriculture. Therefore, the graphene based approach represents an innovative cost-effective alternative towards production of innovative biostimulant of interest and conserving our resources.

In order to stay updated with innovative biostimulant technology, systemic efforts using novel technology like Nanotechnology are required. In the past three decades, the fullerenes, carbon nanotubes and graphene were discovered in 1985, 1991, 2004, respectively and the unique properties of these carbon-based nanomaterials have attracted great interest among the researchers of the engineering, medical, environmental and agricultural fields. A range of carbon-based NMs have gained interest due to their possible applications in regulating seed and plant growth [141]. However, the literature shows both positive and negative effects because of the type of carbon allotrope and concentration, growth conditions and mode of application. Thus, the demands of these nanomaterials have promoted the development of cost-effective methods for large-scale industrial production. Among them, graphene has been recognized most promising carbon nanomaterial instead of fullerenes and carbon nanotubes because of certain reasons such as production ease, cost, toxic nature, and broad-spectrum surface structure attenuation possibilities. Most of the studies have been carried out on the CNTs, CNPs, and fullerenes. Graphene is, basically, a hexagonal crystalline allotrope of carbon consisting of sp2 hybridized carbon atoms with 2-dimensional (2D) properties. The carbon atoms are organized into a hexagonal lattice; each atom has four bonds, one óbond with each of its three neighbours and one ð-bond that is oriented out of plane. Graphene sheets (2D) can be produced using a number of approaches. like mechanical exfoliation and chemical vapour deposition (CVD). However, mechanical exfoliation has poor reproducibility and CVD is a cost-ineffective approach [197, 202, 203]. Therefore, the reduction of graphene oxide (GO) has also been demonstrated to be a comparatively economical and facile technique for the production of reduced graphene oxide (rGO). The GO reduction method of rGO production is a better way for the mass-production of small rGO sheets, while the CVD method is more effective for the mass-production of high-quality rGO to nanoelectronic applications [197, 204, 205], so that the application for which graphene is being synthesized must first be considered before the suitable production method can be selected. GO has many typical characteristics that differentiate it from those of rGO due to the presence of numerous oxygen-containing hydroxyl and epoxy groups and smaller quantities of carboxyl, carbonyl, phenol, lactone, and quinone groups on the basal plane and at the edges, respectively [206-208].

GO is most commonly produced using the Brodie, Staudenmaier, and Hummer methods or some modification of these methods. These methods involve the oxidation of graphite to different amounts, resulting in the formation of hydrophilic groups on the surface. After the oxidation process, the resulting product is then exfoliated to obtain one or multilayered GO sheets with ultrasonication treatment [207, 209]. It is necessary to reduce the GO further to produce rGO through removal of the oxygen-containing groups from the basal planes and edges [210, 211]. Such reduction approaches for rGO production can be physical, chemical and biological in nature [212, 213]. Recently, usage of biological approaches for production of rGO has gained much attention due to their eco-friendly nature, high stability, lower energy requirements, renewablability and cost effectiveness. The microbes like bacteria, fungi etc. have been used for the biological synthesis of rGO from GO. The reduction of GO differs based on the type of microbe used, and different microbes will produce various C: O ratios and chemical composition [214-216]. Biologically produced rGO 2D matrix offers many appealing properties, such as improved biocompatibility and provides an excellent bio-functionalized surface for plant biostimulant immobilization, which contains primary carboxyl and amine groups. There have been numerous reports demonstrating the importance of graphene immobilized biomolecules for innovative applications in biomedicine (targeted drug and gene delivery) and environment. Among the nano allotropes, graphene-based hybrid materials (MNP or biomolecules) have fallen in line with the biocompatibility. The difficulty in scaling up bulk production of rGO has been the limiting factor for its utilization in agriculture field. However, very limited research has been done on the effect of graphene on seeds, especially produced by the microbial approach. Development of biological approaches and self-assembly approaches for the production of rGO analogues has opened-up new avenues for graphene based biostimulant agri-input products, particularly for dry land agriculture. The high surface area and abundance of functional groups present make biologically produced rGO an attracting material in agriculture for efficacious and smart delivery of agri-inputs. So, what makes graphene different? Recent studies have demonstrated beneficial and stimulatory effects of graphene on plants in vitro or in culture conditions [199-201]. Zhang *et al*. [200] observed that graphene at a low concentration affected tomato seed germination and seedling growth. Graphene-treated seeds germinated much faster than control seed because of the facilitation of water uptake. Yijia *et al.* [217] demonstrated the water-transporting properties of GO to promote germination and growth of spinach and chive in soil. It was found that a low dose of GO significantly promoted the germination and growth by increasing the availability of the water to seed. These findings have increased interest in potential applications in sustainable agriculture, although the findings are at the primary level.

Graphene jumped to prominence during the past few years when Geim and Novolosev reported the pristine graphene for the first time utilizing the 'Scotch Tape method' [202, 203]. This innovation of easily obtaining graphene with unique properties to be determined and reported the remarkable high charge-carrier mobility of 2000–5000 cm2/V s [218]. Thus, the authors were duly awarded the Nobel Prize for physics in 2010 for their pioneering work regarding two-dimensional atomic crystals of carbon allotrope [218, 219]. Though, none of the above findings describe the unique properties of graphene; hence it was the combination of the simple method and provoked the scientific community and that was graphene research for innovative and futuristic technologies. However, graphene precursor 'graphene oxide' was synthesized in the late 1950s by Hummers, in 1898 by Staudenmaier , and prior to that in 1859 by Brodie [220]. In the recent years, focus was switched to exploring the approaches for synthesis of graphene or reduced graphene (rGO), others to modifying the structure in a manner that could produce beneficial changes in its properties. The method of production quickly became a relevant problem with graphene as the original 'Scotch Tape method' can only isolate small amounts of graphene and is a laborious and tedious process [212]. Although considerable progress has been made in graphene research and lots of work remain to develop applications for society, graphene have been announced to be the material of the century and its unique properties have been used for various interdisciplinary applications in science and technology fields, ranging from physics to agriculture [195, 213]. Because of nanocarbon material allotropes, exposure studies have demonstrated beneficial and stimulatory effects on plants [141]. These findings have increased interest in potential applications of nanocarbon allotropes in agriculture [192, 196, 204]. In past few years, various nanocarbon material allotropes (e.g., Fullerenes, carbon NPs, SWCNT/MWCNT and graphene) have recently gained interest due to their possible applications in promoting plant growth [141, 195, 221]. The plant growth promoting effects are mainly depending upon type of nanocarbon and concentration, growth conditions, and plant species etc. [196, 222]. The application of water soluble carbon nano-dots have been reported to enhance the root growth (10x) of wheat after 10 days treatment at 150 mg/L dose [223]. The 40–160 µg/L MWCNT dose reported ~50 and 32% increase in root length of wheat seedlings after 3 and 7 days of treatment, respectively [224]. MWCNTs affected seed germination, growth, and the development of barley, soybean and corn. Early seed emergence and a growth in exposed seedlings was observed when MWCNTs were added to sterile agar medium [225].The study demonstrated that MWCNTs have the ability to enhance the growth of tobacco cell culture (55–64% increase over control) in a wide range of concentrations (5–500 µg/mL) and activated carbon (AC) stimulated cell growth (16% increase) only at low concentrations (5 µg/mL), while dramatically inhibited the cellular growth at higher concentrations (100–500 µg/mL) [226].

SWCNTs have also been proven to efficiently cross the cell wall and membranes of tobacco cells upon in vitro exposure, with subsequent transport to specific cellular organelles; this could be taken as evidence for potential use as "nanocarriers" [227, 228]. Compared to the increasing reports on nanocarbon allotropes, limited research has been conducted on the application of graphene in agriculture. The study showed that GO exposure at 0.1 g/L enhanced the activity of anaerobic ammonium-oxidizing bacteria by 10%, along with dose-dependent (0.05–0.1 mg/mL) enhanced production of protein and carbohydrate [229]. Graphene application (500 to 2,000 mg/L) reduced the number and size of leaves of in the cabbage, tomato, and red spinach, which were associated with increased ROS and cell death as well as visible symptoms of necrotic lesions [230]. The adverse effects largely depend on the application dose, surface chemistry and plant type. In another study, effect of engineered carbon nanomaterials like CNTs, C60 and graphene were reported on the germination of rice seeds. A noticeable increase in the seed germination was observed for rice seeds in the presence of applied carbon nanoallotropes. Increased water content was observed in the carbon nanomaterial treated seeds during germination as compared to control. The germinated seeds were grown in a basal growth medium supplemented with carbon nanomaterials for studying their impact on further seedling growth. Treated seedlings appeared to be healthier with well-developed root and shoot systems compared to control seedlings [231]. The enhanced germination viz. 26.6, 43.4, and 13.5% at 2, 4, and 6 days/ respectively of tomato seeds with 40 µg/ml graphene dose [200] has been observed. A novel and biocompatible hydrated graphene ribbon (HGR) was produced and its application unexpectedly promoted germination by 15% root differentiation between 52 and 59% and enhanced resistance to oxidative stress in two years' aged seeds [199].

All to gather, carbon nanoallotropes material applications in agriculture showed very promising results. These nanoallotropes have multifarious effect on crop through the following mode of action; (i) promoting seed emergence and growth (ii) nutrient as well as water adsorption from soil particles and transport and (iii) enhancement growth of soil or rhizosphere microbes. However, in some reports, carbon nanoallotropes did not found to show a positive effect on seed germination in many plants and showed phytotoxicity in plant cells [195]. This could be due to the intrinsic nature of nanoallotropes, like higher application dose and surface chemistry and crop nature like plant type and their growth stages.

Various methods of graphene synthesis using the green and biological routes have developed. The produced graphene was analyzed for the surface functalization (hydrophobic and hydrophilic) as well as structural, optical, elemental, thermal and electrical properties characterized by standard techniques. In addition, range of graphene-based nanocomposites using the green methods and synthesized nanocomposites materials were used for the biomedical and environmental applications [232-236].This technology can introduce a new use of *in-situ* biologically produced reduced graphene for rainfed/dryland agriculture, where cultivation of crops is suffering on account of poor seed germination due to unavailability of critically important moisture.

4. Use of nanoparticles for yield enhancement

This is an area where extensive research has been carried out in the last two decades, and numerous examples are available in the literature [237]. Nanoparticles have shown to improve yield in many crops, including wheat [238], black-eyed peas [239], mung bean [240] and chickpea [241]. A noteworthy point here is that there are only few instances where a nanoparticle itself contributes as micronutrients. Nanoparticles are most effective as a coating material, which allows either better absorption of other nutrients, or convert a macronutrient into a 'slow releasing' one. The latter has been mentioned in countless literature in the last few years and holds tremendous market potential for yield improvement. A non-exhaustive list of such nanoparticles should include silica [242], carboxymethyl (CM) [243], hydroxyapatite [244], chitosan [245], and ZnO [246]. Liu et al. have even successfully made a large tablet consisting of urea and nanosilica, ready for trials [242]. Nonetheless, Zn nanoparticles have a better potential to work with urea, as the conjugate may play a dual role of nitrogen fertilizer as well as a Zn supplement under drought stress conditions.

5. Use of nanoparticles in crop protection

Loss of yield due to abiotic and biotic stresses is a major concern for farmers. Nanoparticles can be more effective than conventional chemical pesticides. Many nanoparticles have shown antibacterial, antifungal, and even insecticidal properties, without compromising on the normal physiology of the host. Environmental pollutants, on the other hand, can also lead to yield loss. There are various examples of nanoparticles facilitating a crop to grow better under abiotic stress conditions. We would only mention some recent examples dealing with very important crops here. Belava et al. [247] have shown that Ag and Cu nanoparticles can protect wheat crop from pathogens, but only by enhancing the plant's internal responses against the pathogen. Hussain et al. has shown positive impacts of iron oxide nanoparticles (Fe NPs) on the alleviation of toxic effects of cadmium (Cd) in wheat [248]. Green-synthesized ZnO nanoparticles have been shown to protect rice against the pathogens [249, 250]. Spagnoletti et al. [251] even used the fungus *Macrophomina phaseolina* for a low-cost method of green synthesis to obtain stable silver–silver chloride nanoparticles with potent antibacterial properties. Much like slow-release fertilizers, slow-release pesticides can also be designed to lower the pollution levels [252]. Apart from protecting a growing crop against pests, nanoparticles can also protect crops during storage. Das et al. [253] reported that oxide nanoparticles can effectively control a major stored grain pest, *Sitophilus* *oryzae* and has the potential to provide a viable alternative to the commercially available insecticides.

Though claimed to be safe by some schools of thought, serious concerns have been raised about the use of nanoparticles in recent literature [254, 255]. Many nanoparticles with antibacterial properties may also simultaneously change the microbial community of the soil and hence, adversely affect many beneficial plant–microbe interactions [256, 257]. Toward this end, biodegradable nanoparticles can become biopesticide of choice. Chitosan nanoparticles [258, 259] have shown effectiveness in the area of crop protection.

6. Use of nanoparticles in protection of environment

Nanotechnology has the potential to revolutionize the agriculture and play an important role in food and crop production. Today, it has become important to increase crop production to feed the growing world population. To meet this increasing demand, researchers are trying to develop an efficient and ecofriendly production technology based on the innovative techniques to increase seedling vigour and plant establishment through physical seed treatments. Seed germination is an important phenomenon in modern agriculture because it is a thread of life of plants that guarantee its survival. Compared with the use of whole plant extracts and plant tissues, the use of plant extracts for making nanoparticles is simpler. Plant extract mediated synthesis is an increasing focus of attention. Processes for synthesising nanoparticles using plant extracts are readily scalable and may be less expensive compared with the relatively expensive methods based on microbial processes.

Synthesis of metal nanoparticles using plant extracts is very cost effective and therefore, can be used as an economic and valuable alternative for the large-scale production of metal nanoparticles. The extracts from plants may act both as reducing and capping agents in nanoparticle synthesis. The percentage of germination and growth was increased by Silica nanoparticles in broad bean [260]. Similarly, positive impact of Si nanoparticle on seed germination potential was observed in tomato [261]. Ghodake *et al.* [262] observed phytotoxicity in *Allium cepa,* induced by application of Cobalt and ZnO NPs; possibly these nanoparticles penetrated radically so that they got adsorbed and accumulated in the root system and damage the cellular metabolism and stages of cell division. Therefore, overall profile of nanoparticles is quite unpredictable and poorly understood. Nano-TiO_2 treatment, in proper concentration accelerates the germination of the aged seeds of spinach [93] and wheat [263] in comparison to bulk TiO_2. Similarly, carbon nanotubes improved seed germination and root growth by penetrating the thick seed coat of tomato and support water uptake inside seeds [192]. The effect of NPs on plants varies from plant to plant and species to species. In order to promote sustainable nanoagriculture, biocompatible silver nanoparticles (AgNPs) have been synthesized through green route using kaffir lime leaf extract for use as a nanopriming agent for enhancing seed germination of rice aged seeds [264]. Shankar *et al.* [265] reported the biosynthesis of pure metallic nanoparticles of silver and gold by the reduction of aqueous Ag+ and $AuCl_4^-$ ions and also the synthesis of bimetallic core-shell nanoparticles of gold and silver by simultaneous reduction of aqueous Ag+ and $AuCl_4^-$ ions with the broth of neem leaves (*A. indica*). They observed that the metal particles were stable in solution even 4 weeks after their synthesis. Moreover, stabilizing the nanoparticles was possibly facilitated by reducing sugars and/or terpenoids present in the neem leaf broth.

Copper (Cu) nanoparticles were biosynthesized using magnolia leaf extract. When aqueous solutions of $CuSO_4$,5H_2O were treated with the leaf extract, stable copper nanoparticles (40–100 nm) were formed. Foams coated with biologically synthesized copper nanoparticles exhibited higher antibacterial activity against *E. coli* cells [266]. In another study, extracellular production of copper nanoparticles was carried out using stem latex of a medicinally important plant, *Euphorbia nivulia*. The produced nanoparticles were stabilized and subsequently capped by peptides and terpenoids present within the latex. The copper nanoparticles are toxic to adenocarcinomic human alveolar basal epithelial cells (A549 cells) in a dose-dependent manner. It was concluded that the non-toxic aqueous formulation of latex capped copper nanoparticles could be directly used for administration/in vivo delivery of nanoparticles for cancer therapy [267].

During the past decades a number of patents and products incorporating engineered nanoparticles (ENPs) into agricultural practices, e.g. nanopesticides, nanofertilizers, and nanosensors have been developed with the collective goal to promote the efficiency and sustainability of agricultural practices, thus requiring less inputs and generating less waste as compared to conventional products and approaches. Metal and metal oxide nanoparticles are among the most widely used types of ENPs; however, little is known about their environmental fate and effects. In addition, pesticides and fertilizers are widely used to enhance agricultural yields, but one of the major challenges today is the need to control and reduce the intensive use of such agrochemicals. It is well known that these substances can have adverse environmental and social impacts, as well as cause resistance in target organisms. Nanotechnology seems to offer a way to mitigate the harmful effects of pesticides on the environment, as nano-pesticides such as Ag, Cu, SiO2, ZnO and nanoformulations exhibit better broad-spectrum pest protection efficiency as well as reducing water, soil and environmental pollution. Moreover, NPs in agriculture need to be economical, ecofriendly and biocompatible. Non-toxic synthesis of bioengineered NPs for agricultural purpose should be compatible with these requisites. There is shift in focus in the synthesis of nanoparticles from conventional to green synthesis, offering more compatibility in agriculture use with reduced adverse effects (Table 6). Thus, Innovations in the area of nanotechnology have opened up the new vistas to use them for sustainable agriculture. Some of latest bioinspired nanomaterials for use in food and agriculture have also been listed in table 7.

Table 6. Recent biosynthesized nano-materials.

Biological system	Biogenic nanoparticles (NPs)	Characterization	Features	Note
1.Bacteria				
Pichia fermentans JA2	Silver and zinc oxide NPs	UV–vis, XRD, and FE–SEM–EDX analysis	Silver NPs inhibited most of the $G^{''}$ clinical pathogens; ZnO NPs inhibited *Pseudomonas aeruginosa* only.	Showed synergistic effect with antibiotics [268].
Bacillus cereus strain HMH1	Magnetic iron oxide NPs	29.3 nm. FE-SEM, DLS, VSM, UV–vis, FT-IR and EDS	Low cytotoxicity: $IC_{50,\ MCF\text{-}7}$>5 mg/ml and $IC_{50,\ 3T3}$ / >/ 7.5 mg/ml	Capping and stabilizing agents [269].
Serratia sp. *BHU-S4*	Silver NPs	TEM (10–20 nm), XRD, EDXA, FTIR	As fungicide against phytopathogen, *Bipolaris sorokiniana* causing spot blotch disease in wheat	Reduction and stabilization [270].
2. Fungi				
Saccharomyces cerevisiae	Silver NPs	UV–vis, XRD, TEM, FTIR	Photocatalytic degradation of methylene blue	Biomolecules as reducing and capping agent [271].
Aspergillus flavus TFR 7	TiO_2 NPs	TEM (12–15 nm), EDX, DLS	Stimulate plant growth: shoot length (+17%), root length (+49.6%), root area (+43%) and root nodule (+67.5%). Promote rhizospheric microbes	Fungi directly isolated from rhizosphere soil [272].
Aspergillus flavus and *Emericella nidulans*	Silver NPs	Hexagonal- and triangular-shaped. DLS (36–531 nm, 37–340 nm), XRD, TEM (30–150 nm, 10–450 nm), FTIR, EDX	Synergistic antibacterial and antibiofilm activity	Reducing and capping agent [273].
3.Yeast				
Candida lusitaniae	Silver/silver chloride NPs	UV–vis, XRD, TEM (13.4 ± 14.5 nm and 6.9 ± 4.5 nm), FIB/SEM, SEM-EDS	Antimicrobial activity	Yeast isolated from termite gut [274].
Magnusiomyces ingens LH-F1	Gold NPs	UV–vis, DLS (137.8 ± 4.6 nm), TEM (80.1 ± 9.8 nm), SEM, SDS-PAGE, FTIR	Catalytic reduction of nitrophenols	Reducing, stabilizing/ capping agent [129].

Contd...

Biological system	Biogenic nanoparticles (NPs)	Characterization	Features	Note
Cryptococcus laurentii and *Rhodotorula glutinis*	Silver NPs	UV–vis, TEM (15–220 nm), XRD, FTIR	Antifungal activity against phytopathogenic fungi (*Botrytis cinerea*, *Penicillium expansum*, *Aspergillus niger*, *Alternaria* sp., and *Rhizopus* sp.)	Yeast isolated from apple peel [275].
4. Actinomycetes				
isolate VITBN4	CuO NPs	UV–vis, TEM (61.7 nm), DLS (198 nm), SEM, EDX, FTIR, XRD (61.7 nm)	Antibacterial activity against human and fish bacterial pathogens	Isolated from soil samples. reduction, capping and stabilization [276].
Streptomyces sp. strain NH21	Silver and gold NPs	UV–vis, TEM (44 ±9 nm for supernatant and 8.4 ± 12 nm for biomass synthesized particles), AFM, FTIR	Antibacterial activity	Isolated from acidic soil. Capping agent [277].
5. Enzyme				
alpha amylase	TiO_2 NPs	XRD, TEM, FTIR	MIC of 62.50 µg/ml on *Staphylococcus aureus* and *Escherichia coli*	Enzyme as reducing and capping agent [278].
6. Plant extracts				
Coffea arabica seed	Silver NPs	DLS (20–30 nm), UV–vis, XRD, TEM, SEM–EDXA, FTIR	MIC ≤ 0.2675 mg/L on *E. coli* and *S. aureus*	[279]
Red ginseng root	Silver and gold NPs	UV–vis, TEM (10–30 nm), EDX	Antimicrobial activity	Reduction and stabilization [280].
Aloe vera plant	Nanoscale zero-valent iron	FESEM, EDS, XRD, FT-IR and TGA	Removal of arsenic (As) and selenium (Se) from water	Plant extract as reducing agent [281].
Cassia tora leaf	Silver NPs	XRD, FTIR, SEM and EDAX	antioxidant and antibacterial activities	Plant extract as reducing agent [282].
Nigella sativa leaf	Silver NPs	15 nm, UV–vis, FTIR, SEM	Lower cytotoxicity and phytotoxicity than wet-chemistry synthesized ones (30 nm)	Plant extract as reducing and capping agent [283].
Atrocarpusaltilis leaf	Silver NPs	SEM (34 nm), TEM (38 nm) and DLS (162.3 nm), FTIR, XRD and EDX	Antimicrobial and antioxidant activity	Phyto constituents as capping agent [284].
Butea monosperma leaf	Gold and silver NPs	DLS, UV–vis, XRD, TEM, XPS, FTIR	Inhibition of cancer cell proliferation	Plant extract as reducing, stabilizing/capping agent [285].
Pineapples and oranges fruits	Silver NPs	UV–vis, SEM (10–300 nm)	N/A	Reducing agent [286].
Longan fruit	Silver NPs	UV–vis, TEM (4–10 nm), XRD, EDX, FTIR	Enzymatic browning reduction on white cabbage. MIC 31.25 µg/ml against *Staphylococcus aureus* and *Basillus subtilus*, 62.5 µg/ml against *Escherichia coli*.	Reducing, stabilizing/capping agent [287].
Butea monosperma bark	Silver NPs	DLS (98.28 nm), TEM, FTIR, XRD and EDX	Cytotoxic effect on human myeloid leukaemia cell line and antibacterial activity	Reducing and capping agent [288].
7. Marine algae				
Macroalga *Sargassum muticum*	ZnO NPs	30–57 nm. FESEM, UV–vis, XRD, FTIR	N/A	[289]
Brown alga *Cystoseira trinodis*	CuO NPs	XRD,AFM, EDX, FE-SEM (6–7.8 nm), TEM (7–10 nm), Raman	Catalytic, antioxidant and antibacterial properties	Reducing, stabilizing [290].

Table 7. Recent bioinspired nano-materials

Bioinspired template	Nanomaterials	Characterization	Features	Note
Mussel	Mussel avermectinNPs [P(St–MAA)–Av–Cat]	120 nm in diameter.	As nanocarrier for controlled release of avermectin and protection against UV light. Higher toxicity towards aphids.	Show potential to enhance folia retention [291].
Cactus	$ZnSnO_3$ Nanostructures	BET (29.2 m^2 g^{-1}), TEM (30–50 nm in diameter)	High-performance humidity nanosensors	Show potential in humidity monitoring [200].
Silk	Graphene	N/A	Battery-free sensors for remote monitoring of pathogenic bacteria at single cell level	Shed light on wireless nanosensors for food pathogen detection [292].
Biological cilia	Polyvinylidenefluoride piezoelectric nanofiber	N/A	Flow velocity and flow direction	May assist in taste sensors or real-time sensing in food safety [293, 294], such as food pathogen [295], allergens [296] and food quality monitoring [297].
Mussel	Polydopamine (PDA)-coated molecularly imprinted SiO_2 NPs	TEM (<–85 nm)	Specific recognition of the trace quantities of papain with low detection limit of 0.63 nM	Show potential in bio analysis in nutritional and dietary supplement [298].
Zwitterion	Fluorescent biomimetic carbon quantum dots	DLS (4.65 nm)	Detection limit for vitamin B12 at 81 nM; highly biocompatible	Show potential in bio analysis in nutritional and dietary supplement [299].
Insect tentacles	Nanoporous Prussian blue (PB) nanocube heads/ TiO_2 nanowire (NW) arms	TEM (diameter and interspacing between adjacent NWs are ~100 and 150 nm)	Sensitive detection of H_2O_2 at a low detection limit (~20 nM), broad detection range (10^{-8} to 10–5 M), short response time (~5 s) and long-term biocatalytic activity (up to 6 months).	Show potential for biomolecule detection in food safety [300].

7. *Nanobiosensors enabled monitoring for sustainable and smart agriculture*

As stated above, productivity in a sustainable manner can only be increased if we embrace the 'smart' agriculture system where soil health (nutritional qualities), soil microbiome community structure, presence of pests, and quality of crops as they develop in field are detected in real time. The detection of these is still possible in conventional methods, but not in real time. In most of the cases, by the time these problems are identified, it is too late for the farmer to take a corrective step ultimately leading to financial loss. Not only real-time detection, but simultaneous relay of these data to the farmer's laptop is also needed for a timely action. Nanobiosensors can provide excellent product solution in this sector. The presence of a pest is usually investigated only after the symptoms are observed. On top of that, PCR-based methods are currently employed by scientists. This can be time consuming, and adds a PCR bias for over-represented species in mixed samples. Dextrin-capped gold nanoparticle has been shown to detect pathogen DNA (probe based), even without being amplified by PCR [301]. More than one method of immunogenic detection of pathogen by nanosensors are also available [302, 303]. Nanosensors have been successfully shown to convert a living spinach plant to an auto-sampler which relays the information through IR, or a plant can be engineered to emit light signals depending on the environment [304, 305]. Real-time analysis of glucose and sucrose in plants is also possible [258, 306]. Biosensors have been designed to detect toxic pesticides and heavy metals in soil. Printed graphene electrochemical biosensors [307] can effectively detect organophosphates in soil samples. Similarly, G-quadruplex DNA and gold nanoparticles conjugate have been shown to detect Pb^{2+} in soil [308]. Molecularly imprinted sol-gel-coated Au nano-urchin sensors can sense plant volatile compounds like jasmonic acid [309]; much like other nanocomposite sensors could also be built to detect ethylene. Even a smart phone-based handheld VOC fingerprinting platform has recently been designed using plasmonic Cys-capped gold nano-colorants and chemo-responsive organic dyes [310]. These sensors will definitely enable us to detect many volatile biomarkers of plant health, much before a farmer starts seeing the visual effects.

Regulating the Use of Nanotechnology

Nanoparticles should be used wisely and stringently screened before environmental release. There is a false notion of all these nanoparticles being safe. In fact, many nanoparticles have shown toxic effects, including green-synthesized nanoparticles [311]. Some of them used as antimicrobial agents can severely harm the entire soil microbiome, which can have adverse effects on productivity [312]. A neem oil-based non-metal nanoparticle has been developed recently, which can soon become the pesticide of choice [313]. Finally, the dynamics of interaction between a plant tissue and a nanoparticle must be assessed before any commercial use. Thankfully, excellent methods of in vivo delivery of quantum dots into whole plants have been standardized, which will ease confocal microscopic and biochemical studies of the above-mentioned interaction [314].

Regulations and Legislations Governing Nanoparticles

Regulation and legislation play a fundamental and key role for the implications of nanotechnology as well as marketing of products. They also serve as official sources and references for public knowledge and awareness. Normally, there are three main steps to legislate. 1) Suggestions are firstly made by academic parties (can be research institutes, organizations, government agencies or even individuals). 2) Reasonable suggestions are taken by a government agency (sometimes named guidance) and are proposed (by head of a state/country or a legislative body) as a directive, known as legislation. Legislation is then passed by a parliament of a country or other legislative arm of a government and becomes a law. 3) Legislation (or law) usually covers broad and general aspects pertaining to an industry. Thus, when it is enforced by regulators, regulations are generated, referring to the detailed and specific requirement that can take on various forms. Regulations are much broader in the scope for a particular industry.

It takes the same procedures to legislate for the nanotechnology in food industry. When nanotechnology in food industry was first proposed, governing agencies were formed or appointed by the relevant governments all over the world. Some are listed in ref. [16]. Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), as the main regulation for Europe Union (EU), is the most active agency concerning legislation of nanotechnology in food industry, followed by Food and Drug Administration (FDA) of USA. Their up to date documents are available at https://europa.eu/european-union/index_en and https://www.fda.gov/default.htm, respectively.

In the past decades, much effort has been put into legislation, which has been extensively reviewed in previous publications [315-321]. Identification and expression by different agencies may vary, but they share the common basic concepts, for instance, nanotechnology deals with materials with at one dimension lying within 100 nm. Some key updates are listed in table 8.

The calls for tighter regulation of nanotechnology have occurred alongside a growing debate related to the human health and safety risks of nanotechnology [327]. There is significant debate about who is responsible for the regulation of nanotechnology. Some regulatory agencies currently cover some nanotechnology products and processes (to varying degrees) – by “bolting on” nanotechnology to existing regulations - there are clear gaps in these regimes [328]. Davies [329] has proposed a regulatory road map, describing steps to deal with these shortcomings.

The stakeholders concerned by the lack of a regulatory framework to assess and control risks associated with the release of nanoparticles and nanotubes have drawn parallels with bovine spongiform encephalopathy (“mad cow” disease), thalidomide, genetically modified food [330], nuclear energy, reproductive technologies, biotechnology, and asbestosis. Dr. Andrew Maynard, Chief Science Advisor to the Woodrow Wilson Centre’s Project on Emerging Nanotechnologies, concludes that there is insufficient funding for human health and safety research, and as a result there is currently limited understanding of the human health and safety risks associated with nanotechnology [331]. As a result, some academics have called for stricter application of the precautionary principle, with delayed marketing approval, enhanced labelling and additional safety data development requirements in relation to certain forms of nanotechnology [332].

The Royal Society report [333] identified the risk of nanoparticles or nanotubes being released during disposal, destruction and recycling, and recommended that “manufacturers of products that fall under extended producer responsibility regimes such as end-of-life regulations publish procedures outlining how these

Table 8. Some of the key regulations and legislations governing nanoparticles

Year	Policy (change/update)	Reference
2011	"Official" definition of nanomaterial.	EU Commission Recommendation [120], available at https://ec.europa.eu/research/ industrial_ technologies/pdf/policy/commission-recommendation-on-the-definition-of-nanomater-18102011_en.pdf
2011	Provide data on the stability of the nanomaterials in the proposed formulations and under the proposed conditions of use (in feed).	FDA final guidance [322], available at https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM401508.pdf
2012	Mandatory labelling for nano-ingredients in food introduced in labelling Regulation, Labelling applicable from December 2014	Second Regulatory Review on Nanomaterials [323], available at https://eur-lex.europa.eu/ legal- content/EN/TXT/PDF/ ?uri= CELEX :52012 DC0572&from=EN
2012	Evaluation of REACH registration dossiers concerning nanomaterials prioritised by ECHA for compliance check. Substance of the "CoRAP" list includes silicon dioxide (NL 2012), silver (NL 2013) and titanium dioxide (F 2014).	Second Regulatory Review on Nanomaterials [323]
2012	Assess the coverage of nanomaterials in environmental legislation, such as waste, water and air legislation.	EU MEMO [324], available at http://europa.eu/rapid/press-release_MEMO-12-732_en.htm?locale=en
2012	Case-by-case safety evaluation for nanomaterials.	EU Press Release [325], available at http://europa.eu/rapid/press-release_IP-12-1050_en.htm?locale=en
2014	FDA does not categorically judge all products containing nanomaterials (or involving application of nanotechnology) as intrinsically benign or harmful.	Final guidance for industry [326], https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM616225.pdf
2017	Taiwan FDA considers nanomaterials as new food contact substances and enforces food packaging nanomaterials to go through safety assessment and obtain pre-market approval.	Taiwan FDA guidelines (in Chinese), available at https://www.fda.gov.tw/TC/newsContent.aspx?id=21901&chk=8b47bc84-e1c1-4c36-b410-4ff637bf7f05&param=pn&cid=3&cchk=46552e96-810a-42c3-83e1-bd5e42344633#.W Mqh0 zuLS71

materials will be managed to minimize possible human and environmental exposure". The Center for Nanotechnology in Society has found that people respond to nanotechnologies differently, depending on application – with participants in public deliberations more positive about nanotechnologies for energy than health applications, suggesting that any public calls for nano regulations may differ by technology sector [334].

Implications of Nanotechnology

An area of concern is the effect that industrial-scale manufacturing and use of nanomaterials (Table 9) would have on human health and the environment, as suggested by nanotoxicology research. For these reasons, some groups advocated that nanotechnology be regulated by governments. Others counter that overregulation would stifle scientific research and the development of beneficial innovations. Public health research agencies, such as the National Institute for Occupational Safety and Health are actively conducting research on potential health effects, stemming from exposure to nanoparticles [335, 336]. Some nanoparticle products may have unintended consequences.

Researchers have discovered that bacteriostatic silver nanoparticles used in socks to reduce foot odour are being released in the wash [56]. These particles are then flushed into the waste water stream and may destroy bacteria which are critical components of natural ecosystems, farms, and waste treatment processes [337]. Public deliberations on risk perception in the US and UK carried out by the Center for Nanotechnology in Society found that participants were more positive about nanotechnologies for energy applications than for health applications, with health applications raising moral and ethical dilemmas, such as cost and availability [334].

Experts, including director of the Woodrow Wilson Centre's Project on Emerging Nanotechnologies; David Rejeski have testified [338] that successful commercialization depends on adequate oversight, risk research strategy and public engagement. Berkeley, California is currently the only city in the United States to regulate nanotechnology [339]; Cambridge,

Table 9. Use of different nanoparticles by various sectors/industries

Sector	Nanoparticles
Agriculture	Silver, silicon dioxide, potassium, calcium, iron, zinc, phosphorus, boron, zinc oxide and molybdenum
Automotive	Tungsten, disulfide silicon dioxide, clay, titanium dioxide, diamond, copper, cobalt oxide, zinc oxide, boron nitride, zirconium dioxide, tungsten, ã-aluminium oxide, boron, palladium, platinum, cerium (iv) oxide, carnauba, aluminium oxide, silver, calcium carbonate and calcium sulfonate
Construction	Titanium, dioxide, silicon dioxide, silver, clay, aluminium oxide, calcium carbonate, calcium silicate hydrate, carbon, aluminium phosphate, cerium (iv) oxide and calcium hydroxide
Cosmetics	Silver, titanium dioxide, gold, carbon, zinc oxide, silicon dioxide, clay, sodium silicate, kojic acid and hydroxy acid
Electronics	Silver, aluminum, silicon dioxide and palladium
Environment	Silver, titanium dioxide, carbon manganese oxide, clay, gold and selenium
Food	Silver, clay, titanium dioxide, gold, zinc oxide, silicon dioxide, calcium, copper, zinc, platinum, manganese, palladium and carbon
Home appliance	Silver, zinc oxide, silicon dioxide, diamond and titanium dioxide
Medicine	Silver, gold, hydroxyapatite, clay, titanium dioxide, silicon dioxide, zirconium dioxide, carbon, diamond, aluminium oxide and ytterbium trifluoride
Petroleum	Tungsten, disulfide, zinc oxide, silicon dioxide, diamond, clay, boron, boron nitride, silver, titanium dioxide, tungsten, γ -aluminium oxide, carbon, molybdenum disulfide and γ -aluminium oxide
Printing	Toner, deposited by a printer on paper or other substrate
Renewable energies	Titanium, palladium, tungsten disulfide, silicon dioxide, clay, graphite, zirconium(iv) oxide-yttria stabilized, carbon, gd-doped-cerium (iv) oxide, nickel cobalt oxide, nickel (ii) oxide, rhodium, sm-doped-cerium (iv) oxide, barium strontium titanate and silver
Sports and fitness	Silver, titanium dioxide, gold, clay and carbon
Textile	Silver, carbon, titanium dioxide, copper sulfide, clay, gold, polyethylene terephthalate and silicon dioxide

Massachusetts in 2008 considered enacting a similar law [340], but ultimately rejected it [341]. Over the next several decades, applications of nanotechnology will likely include much higher-capacity computers, active materials of various kinds, and cellular-scale biomedical devices [342].

Health and Environmental Concerns

Nanofibers are used in several areas and in different products, in everything from aircraft wings to tennis rackets. Inhaling airborne nanoparticles and nanofibers may lead to a number of pulmonary diseases, e.g. fibrosis [343]. Researchers have found that when rats breathed in nanoparticles, the particles settled in the brain and lungs, which led to significant increase in biomarkers for inflammation and stress response [344] and that nanoparticles induce skin aging through oxidative stress in hairless mice [345, 346]. A two-year study at UCLA's School of Public Health found lab mice consuming nano-titanium dioxide showed DNA and chromosome damage to a degree "linked to all the big killers of man, namely cancer, heart disease, neurological disease and aging" [347, 348].

A major study published more recently in Nature Nanotechnology suggests some forms of carbon nanotubes – a poster child for the "nanotechnology revolution" – could be as harmful as asbestos, if inhaled in sufficient quantities. Anthony Seaton of the Institute of Occupational Medicine in Edinburgh, Scotland, who contributed to the article on carbon nanotubes, said "We know that some of them probably have the potential to cause mesothelioma. So, those sorts of materials need to be handled very carefully [349]. In the absence of specific regulation forthcoming from governments, Paull and Lyons [350] have called for an exclusion of engineered nanoparticles in food. A newspaper article reports that workers in a paint factory developed serious lung disease and nanoparticles were found in their lungs [351, 352].

Safety Concerns

Experts feel that the potential benefits of nanotechnology for agriculture, food, fisheries, and aquaculture need to be balanced against concerns for the soil, water, and environment and the occupational health of workers. Raising awareness of nanotechnology in the agri-food sector, including feed and food ingredients, intelligent packaging and quick-detection systems, is one of the keys to influencing consumer acceptance. On the basis of only a handful of toxicological studies, concerns have arisen regarding the safety of nanomaterials, and researchers and companies will need to prove that these nanotechnologies do not have more of a negative impact on the environment. In terms of global food and livestock production, main aspects of nanotechnology are improved quality and nutritional value. In spite of potential benefits that nanotechnology offers in the agri-food sector (food production, feed for livestock, food ingredients, packaging, and nanobased smart systems), little is known on safety aspects of application of nanotechnologies in food production and the incorporation of nanoparticles in food. Moreover, consumers still lack knowledge about nanotechnology.

Risk-assessment procedures are not specific to agri-food nano-materials, resulting in uncertainty regarding the nature and extent of potential risks in most cases. The applications of nanomaterials currently used for meat, and food generally, include the use of nanoparticles and nanomaterials as food ingredients/ additives that are placed directly into food or as a part of food packaging [353]. There is a need to pay attention to public views regarding new technologies in the food business during the product development stage to avoid some of the pitfalls encountered by the genetically modified food industry [354]. The release of engineered nanoparticles may cause adverse effects on edible plants [355]. The potential risks and benefits of using nanosilver as an antibacterial agent in consumer and health care products are being debated globally [356].

Elevated cerium content was detected in plant tissues exposed to cerium oxide nanoparticles, suggesting that cerium oxide nanoparticles were taken up by tomato roots and translocated to shoots and edible tissues. In particular, substantially higher cerium concentrations were detected in the fruits exposed to 10 mg $L^{"1}$ cerium oxide nanoparticles, compared with control. This study sheds light on the long-term impact of cerium oxide nanoparticles on plant health and its implications for our food safety and security [357]. Lack of regulatory harmonization and empirical data are impeding global strategies for product commercializing nanotechnologies [358]. Thus, there is an urgent need for regulatory systems capable of managing any risks associated with nanofoods and the use of nanotechnology in the food industry [359].

In 2012, a new biocidal product regulation (EU 5 28/2012) was adopted in the European Union. The regulation specifically requires assessment and approval of active nanomaterial biocidal ingredients. The environmental and societal implications of nanotechnology were assessed [360]. The European Parliament Committee on the Environment, Public Health and Food Safety rejected a proposed regulation on February 12, 2014, that intended to define "engineered nanomaterials" in food. Such definition could lead to existing nanomaterials not being labelled due to an exemption provided for food additives approved on a European Union list [361, 362].

Public Awareness and Acceptance

There were cases that silver NPs were added into packaged materials due to their antimicrobial activity and these materials had been widely used in many food (like milk) packaging. The general public consumed these products without knowing the addition of nanoparticles, which could be both an ethical and legislative issue. Now, proper labelling has become mandatory so that public is aware of what they consume. It is the manufacturer's responsibility to keep this information transparent and available to the public.

Public awareness and acceptance is an important part but often ignored by a food manufacturer. In fact, most food manufacturers keep their new product development "underground" and would not like to share with the public (maybe partly due to the competition and trade secret) [363]. This can be a conflict with the fact that the public intends to know what and why the food manufacturer is marketing a new product. The case study in Singapore already proved that unawareness of nanotechnology and its adverse effects of nanotechnology increases negative perception of the public [364]. It is even worse that agri-food organisations (stakeholders) also have a very low awareness with respect to nanotechnology, as reported by a survey on the island of Ireland [365].

Public voice is twofold, assent and dissent (or altruism and skepticism) with nanotechnology in food industry [366]. Public attitude greatly depends on the specific applications. Nanotechnology in food received 49% support in 2005 and 32% in 2008 (which is one of the lowest among all nanotechnology applications), while food packaging applications that monitors condition was supported by 73% of respondents in 2008. The highest concern was expressed regarding the usage of nanotechnology, particular in food (28%) [367]. Using canola oil as an example, according to a nationwide online survey in the U.S., consumers are only willing to pay less for canola oil that is processed or packaged with nanotechnology modified seeds or techniques. No significant difference was found for canola oil with health-enhancing nano-engineered oil drops [368]. It feels that public hold a neutral attitude toward nano-engineered canola oil, whereas nano-engineered canola oil does not present all nano food.

So far "Organic" is likely the most commonly accepted standard for healthy food. Many people prefer traditional and "organic" food, especially when they compare it with genetically modified food. Sometimes, public are even confused by genetically modified food with nano-engineered food [369]. The main cause is the poor access to information and resources of food nanotechnology available in the public domain. Nanotechnology is not yet a matured technique to be used in food industry. Limited evidence from scientific standpoint makes it hard or even unethical to advertise this uncertain technology to the public.

Risks Associated with Exposure of Nano-products

The increasing application of nanotechnology in the food and agriculture sectors has attracted public attention over the past decade. Nanomaterials are either intentionally added as food additives or unintentionally introduced *via* migration [370] in many food and agriculture products. Consequently, concerns over environmental and human health arise as the spread of nano-products expands, owing to the unique physiochemical properties of nanomaterials [371-376]. The concerns over environmental health are a direct consequence from the interaction of nanomaterials used as nanofertilizers, nanopesticides, nanoherbicides, and less likely the immobilized nanosensors. The behaviour and fate of nanomaterials in environment largely depend on the physiochemical properties of the nanomaterials *per se*. Additionally, the complexity of environmental conditions limits the predictability of the behaviour and fate of nanomaterials. It is difficult to trace and monitor the distribution of nanomaterials as a result of the complicated nano-bio-eco interactions [372, 373, 376]. Although holistic approach has been recommended for understanding of the nano-bio-eco interactions between the nanomaterials and biotic and abiotic environments in a connected ecosystem [372]; case-by-case studies are needed for a conclusive assessment of environmental nanotoxicity.

Here, we take the exposure route of aluminum NPs in human digestion system as an example [377] to illustrate the complexity and possible experimental workflow to assess nano-products associated risks. At the initial stage of digestion, samples remain unchanged in artificial saliva. Aluminum NPs begin to partially dissolve and release aluminium ions in stomach fluid. Particle agglomeration may occur any time during the digestions process, but most significantly in stomach fluid. In the intestinal fluid, agglomerates tend to deagglomerate into primary particles. In addition, nanoparticulate structures are formed *de novo* from free ions [377]. The same routine applies to silver NPs. Silver colloids exist in any medium as complicated mixtures with many different species absorbed on the surface [378-380]. This triggers release of Ag^+ ions as both culprit for toxicity [381-383] and as antimicrobial agents for drug-resistant bacteria [148, 384, 385]. Gold NPs can also release Au (I and III) ions in ambient conditions and contribute to downstream interactions [200].

a. Nanotoxicology mechanisms

Human health upon exposure to nanomaterials as food additives and other functional ingredients of food and agriculture products is also of major concerns. The direct contact of nanomaterials used as food additives/functional/nutritional ingredients may pose threats to human health. The production of reactive oxidative species (ROS) acts as one of the main toxicological mechanisms causing cellular damage and death [372]. Overproduction of ROS can lead to autophagy [386], neuron damage [387], and severe damage to DNA [372, 388], and potentially mutagenesis, carcinogenesis, and aging-related diseases in humans. Allergic reactions and damage due to metal ion release from nanomaterials are also possible adverse outcomes upon the exposure to food nano-products [389]. Additionally, the accumulation of nanomaterials in edible parts (seeds) of plants [144] and human body [390] may cause severe problems at a higher concentration and long-term interactions.

The potential risks of traditional nanomaterials are an ongoing debate and are under active research. Hence, more data on risk assessment is definitely required. Additionally, many approaches have been utilized to reduce the toxicity of engineered nanomaterials, and meanwhile, improve the target selection and performing reliability. For example, controlled tailoring on surface functionalization, doping, and morphological (i.e. size and shape) control has been demonstrated as effective approaches to make engineered nanomaterials more sustainable and less toxic.

b. Generating data on risks and analysis

Thorough and accurate assessment of nanotoxicology thus becomes paramount to the safe engineering, handling and use of nanomaterials in food and agricultural products. Moreover, current methodologies typically used for toxicology provide little information that is useful for chemists to improve their sustainable design for large scale use [391]. Aside from many research progresses on cellular damage *in vitro* and *in vivo*, toxicological data is still largely limited to reach any conclusive statement for the general pattern of nanomaterial exposure and toxic impact on human health. The limit at large is due to the complexity of nano-bio-eco interactions as we have discussed elsewhere [372, 373, 376]. The cost is high and the generated data is limited for traditional *in vitro* and *in vivo* analyses focusing on limited endpoints and processes, such as ROS production, DNA damage, immune responses, and many others. Using model organisms and cell lines, such as *Escherichia coli* [392] and human A549 lung adenocarcinoma cell line [393], respectively, for generating omics data is probably the future trend for the study of nanotoxicity. Machine learning approach should be adapted to explore the growing data at the same time.

Future Perspectives

The abilities of crops to efficiently utilize Boron resources vary considerably. Thus, from an agricultural point of view, there is a need to identify the important cultivars of agronomic and horticultural crops with vigorous root systems to utilize the available B and that can thrive best under B shortage. For example, in cucumber, the Ashlay variety performs well under Fe-deficient conditions with high nutrient and chlorophyll content and reduced chlorosis [394]. In rape seed, the B use efficiency is closely related to sugar production [395], earlier flowering, and bolting [396], which certainly reduce the B requirement for vegetative biomass production. The knowledge of the rootstock and scion relationship may be helpful in identifying excellent root systems of crops that are tolerant to deficient or toxic B conditions. Furthermore, the mechanistic investigation at the molecular level for B in plants has opened new prospects to improve B stress tolerance in crops.

Indeed, grafting and AMF inoculation improve plant physiological and nutritional aspects and a number of studies have proved their pivotal role in B uptake [397-400]. Additionally, nanotechnology is an emerging technique to solve plant-nutrition related problems. The combination of these techniques may improve B uptake. For instance, a combination of grafting and Cu NPs improved growth and development of watermelon by increasing ion uptake [89]. The application of melatonin improves plant performance by inducing resistance against stress conditions. According to a report, melatonin application reversed the toxic effect of B by moderating B accumulation in leaf and fruit, increasing photosynthetic activity, and improving dry weight that ultimately enhanced plant growth of *Capsicum annuum* [401]. Similarly, in watermelon, melatonin application enhanced the N concentration in roots by improving root elongation diameter and surface area under limited N availability [402]. However, no evidence for B uptake under deficient conditions has been found yet and need further investigation. A stressful environment exerts a negative impact on plant growth and development. However, this stress can be mitigated by the use of PGPR and AMF. Most studies on MF and rhizobacteria application focused on improving B acquisition and plant growth under normal and stress conditions [403, 404]. Certainly, these applications enhance the water and B content of plants, but the dual inoculation of both MF and PGPR could be more useful in B assimilation compared with their sole application. In some plant species, the combined inoculation of MF and PGPR improved growth by enhancing water and macronutrient content [405]. However, to the best of our knowledge, no data are available for micronutrients, particularly B. The mechanism of nutrient acquisition by these microorganisms is also poorly understood. Therefore, the role of combined inoculation of these microorganisms for efficient B acquisition and its molecular mechanism need to be investigated further to achieve better results and to improve B uptake and utilization in plants.

Nanotechnology exhibits promising potential to be widely utilized in almost every aspect of food industry. This is based on limited knowledge obtained mainly from labs. The practical application of nanotechnology and marketing nanomaterial-based product remains uncertain, considering the poor capability to control properties and interaction of materials at nanoscale, as well as the unclear environmental effects and almost vacant toxicity database. It also limits development of the body of regulation and legislations, further putting obstacles for the marketing of novel nano-products.

Despite the low levels of public awareness to food nanotechnology, their attitude is tunable depending on the way nanotechnology is used and advocated. The conflict seems to be that public wants to be informed on the status of food nanotechnology (especially development of related novel products), while food manufacturers prefer the opposite since their technologies are confidential. For the information of both public and food manufacturers, sufficient database and evidence should be built up, which could serve as logistic support and is the need of the hour.

Since implementing environmentally friendly practices has become more and more essential for success in today's biotechnology business, bioinspired approach is becoming popular in biological researches and many other relevant fields. However, as compared to biomedical fields, currently the research and development of bio-inspired nanomaterials for usage in food and agricultural sectors are rather limited. Driven by the food industry that is a trillion-dollar business, many products involving novel nanotechnology have been marketed all over the world, particularly in the field of food contact materials/ technologies (like packaging materials/monitors). This will continue to be a battlefield for the manufacturers due to safety code control by legislative branch of a government.

The core/shell nanocomposite structures, including magnetic nanoparticles could show potential in crop protection and conjugation with various oxide nanomaterials can further enhance the entomotoxic effects of insecticide/s. Similarly, indirect detection of biomarkers, like H_2O_2 would have high potential to streamline the process of alerting the farmer early, if all these platforms be brought together. Finally, changes in volatile organic compounds (VOCs) following infection by a pathogenic microorganism can be a useful parameter that can be measured in future. Monitoring different parameters of a growing plant's nutritional status can lead to real-time health analysis and assessment of crop productivity.

CONCLUSIONS

As we are in relentless search of technologies that will increase our crop productivity, nanotechnology appears to be an excellent solution. The last decade has witnessed tremendous efforts in research and invention of these technologies. The next decade must be spent to bring these technologies in a cost-effective package. Efforts to translate these solutions from scientific laboratories to the field, and to attract interested investors to facilitate market penetration are still at large. If these hurdles are overcome, the future of nanotechnology in precision agriculture appears bright. The judicious and controlled use of nanotechnology can lead to a sustainable green revolution on Earth.

Many diverse opportunities for nanotechnology exist to play an important role in agriculture, including food and livestock production. The potential uses and benefits of nanotechnology are enormous. Productivity enhancement through nanotechnology-driven precision farming and maximization of output and minimization of inputs through better monitoring and targeted action is desirable. Nanotechnology enables plants to use water, pesticides, and fertilizers more efficiently. The use of nanotechnology may bring potential benefits to farmers through food production and to the food industry through development of innovative products through food processing, preservation, and packaging. Anticipated agri-food nanotechnology applications include nanosensors/nanobiosensors for detection of pathogens, monitoring of plant health and soil quality, nanoporous zeolites for slow-release and efficient scheduling of irrigation and fertilizers for plants and of nutrients and drugs for livestock, nanocapsules for delivery of agrochemicals, creating biofuels, nanocomposites for plastic film coatings used in food packaging, antimicrobial nanoemulsions for applications in decontamination of food, nanobiosensors for identification of pathogen contamination, and improving plant and animal breeding.

Even so, less effort is going into applications of nanotechnology in agri-food sectors. Further, existing efforts are more oriented to reduce the negative impact of agrochemical products in the environment and human health, rather than the utilization of nanotechnology applications to improve their properties for food and livestock production. The experts envision numerous nanoparticulate agro formulations with higher bioavailability, efficacy and better selectivity in the near future. Multidisciplinary approaches could potentially improve food production, incorporating new emerging technologies and disciplines such as chemical biology integrated with nanotechnologies to tackle existing biological bottlenecks that currently limit further developments. The potential benefits of nanotechnology for agriculture, food, fisheries, and aquaculture need to be balanced against concerns for the soil, water, environment and the occupational health of workers. Green synthesis has gained extensive attention as a reliable, sustainable, and eco-friendly protocol for synthesizing a wide range of materials/nanomaterials, including metal/metal oxides nanomaterials, hybrid materials and bioinspired materials. Thus, the agricultural sector and the seed industry might indeed witness tremendous changes for the betterment in the coming years.

We quote from the Trek magazine article: “Nanotechnology could be the first technology developed with sensitivity to ethical, environmental and social issues. If we fearlessly and responsibly examine all aspects of the technology today, we can anticipate our tomorrow will be enriched with benefits.” The benefits of nanotechnology are enormous, with many potential and exciting products on the market. But so too are the challenges, and fundamental questions with regard to high performance, low toxic nanomaterials need to be addressed to fuel active development and applications of nanotechnology. There are major gaps in our understanding of the health, safety, environmental, and societal impacts of nanotechnology. Hence, bridging these gaps will be critically important for the long-term success of nanotechnology. Regulation and legislation are also paramount to regulating the manufacturing, processing, application, as well as disposal of nanomaterials. Further efforts are still needed to strengthen public awareness and acceptance of the novel nano-enabled food and agricultural products. Finally, it is re-emphasized that food and agriculture nanoscience represents a university research culture shift and that filling these gaps will require a multidisciplinary approach and it is of paramount importance that public trust built in the science and industry of nanotechnology. Controversial issues pertaining to nanotechnology have already sparked public interest in the field. Establishing public trust ,developing and maintaining the credibility of nanoscience will require a coherent and rational approach on behalf of the scientific enterprise, careful planning and strategic coordination, and the bringing together of the concerned multidisciplinary teams with a networking mindset. We conclude that nanotechnology offers a plethora of opportunities, by providing a novel and sustainable alternative in the food and agriculture sectors.

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