Ramesh Namdeo Pudake ·
Nidhi Chauhan · Chittaranjan Kole
Editors

Nanoscience for Sustainable Agriculture

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Preface

Agriculture is one of the fundamental sectors that can be never ignored by any society. The industrialization and growing human population have adverse effects on all sectors of agriculture, which may soon be resulting in a reduction in the production of various commodities like food, meat, milk, and so on. The world's population is constantly increasing, while agricultural resources are constantly decreasing due to overexploitation. To meet additional demand for output from agriculture sector which can be sustainable, there is an immediate need for the use of new tools and technologies in all components of agriculture. For sustainable agricultural production in the future, we must be able to develop tools which can reduce the agricultural inputs required for optimum production. Secondly, we need to develop technologies which can reduce the wastage of agricultural products until it reaches to the consumer. For this, the traditional method has been routinely used with little success. An alternative strategy for sustainable agriculture is the use of novel technologies like biotechnology and nanotechnology.

The application of nanomaterials in agriculture sector like input delivery, genetic engineering, animal health, precision farming, food processing industry, and water use has a vast scope. It can be used with the objectives like reduction of pesticides, minimize nutrient losses through optimized nutrient management. The nanomaterials and tools also can be used for quality enhancement and management of food products. It can increase in shelf life of meat and milk products. Devices and tools like nanocapsules, nanoparticles, nanocomposites, and sensors developed through the application of nanotechnology can be used for the detection and treatment of plant and animal diseases, the increase of nutrients absorption by crop plants, the targeted delivery of active ingredients in animals and plants, along with water and timber treatment processes. The usage of targeted delivery and slow-releasing agrochemicals can reduce the damage to non-target organisms and the quantity released into the soil and water. Nanotechnology derived tools are also being explored in the field of plant and animal genetic improvement.

Despite the potential advantages, the application of nanotechnology in agricultural sector is still comparably trivial and has not yet made it to the market in terms of range products that are in health and electronics. Like other technologies, it also has some issues that still need to be addressed. So, there is a need of continuing research in the commercial agrochemical industry to utilize potential future advantages. The concern regarding the regulation and evaluation of safety of nanomaterials also needs to be addressed. The aim of this book is addressing the issue of knowledge gap. It is hoped that this book will interest students and researchers in the lasted outcomes of nanotechnology research in the field of agriculture and allied sciences and encourage the young researchers to explore this promising field. This book contains 27 chapters written by 72 eminent subject specialists that covered the diverse aspects of nanotools for achieving sustainability in agriculture.

We are grateful to many people who directly or indirectly helped to compile this book. We thank Mrs. Christina Eckey and Mr. Naresh Kumar Mani from Springer for their help and patience in finalizing this book. We also like to thank our families, friends, and colleagues for their support during all the activities done during the writing of this book. We especially like to thank Dr. Ashok K. Chauhan, Founder President, Ritnand Balved Education Foundation, New Delhi, for the kind support and encouragement for academic endeavors.

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Part I
Nanomaterials in Crop Science

Chapter 1
Application of Nanotechnology in Genetic Improvement in Crops

M. Sheikh Mohamed and D. Sakthi Kumar

Abstract Plant genetic engineering is at the epicenter of environmental sustainability endeavors, synthesis of natural products of commercial and pharmaceutical value, while also addressing the ever-expanding food and energy requirements of an ever-growing global population impacting the global climate in more ways than one. Though the importance of this field has been emphasized, still progress remains at a slow pace, partly owing to the drawbacks of conventional plant biotransformation approaches such as limited host range, below par transformation efficiencies, cellular toxicity, in addition to foreign DNA integration into the host genome. These drawbacks are additionally supported by the presence of plant cell wall which has been a limiting checkpoint for essential exogenous biomolecules entry. Nanotechnology, with its well-established impact on the materials, electronics, energy, and medical sectors, has found a new role in plant genetic engineering. Nanomaterials with their unique physicochemical properties have attracted immense interest from plant scientists and are the solution to the conventional limitations faced in plant biotransformation. A wide array of nanoparticles have been already studied for carrying and delivering sensitive cargo (DNA, RNA, proteins) to specific cells without any damage to the cargo or the host. This chapter deals with such nanomaterials, their success, challenges and future scope in agriculture.

1.1 Introduction

Increasing global food security triggered by man-made and natural causes has been exerting tremendous pressure on the agricultural sector. The past century was witness to numerous technological innovations, such as the development of hybrid varieties, systemic development, and use of highly efficient synthetic chemicals that helped the growth in crop production (Ray et al. 2013; Fischer et al. 2014).

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However, a major boost was seen with the advent of biotechnology, which propelled the production of crops that were resistant to various biotic and abiotic factors including viruses, pests, drought, salinity, etc. (Altman and Hasegawa 2011). Though all this assisted greatly in addressing the global food management, numerous factors, natural and man-made, have been stalling the progress or alternatively creating sudden and excessive demands, varying by geographic locations, which have been posing new challenges for this sector (FAO 2018). Therefore, rises the need for a more advanced technological system for alleviating the problems faced by the agricultural community which can work in conjunction with the old system (conventional) and independently on its own.

Due to the various revolutionary applications in fields as diverse as medicine, materials science, electronics, energy, etc., nanotechnology has emerged as an indispensable asset in the modern world (De et al. 2014). It is only befitting that it is accredited as one of the six "Key Enabling Technologies" by the European Commission (European Commission Communication 2009). Investigations on the applications of nanotechnology in agriculture pertaining to sustainability, resistant/tolerant varieties, increased productivity, post-processing, packaging, and distribution, etc. have been going on for many years, but has only over the past decade began to take prominence, which is evident from the increased number of scientific publications and patents in this field (Rodrigues et al. 2017; Lowry et al. 2019; Mohamed and Kumar 2016a, b). The essence of nanotechnology lies in minimizing the essentials and delivering them to exactly the desired location with high precision, thus greatly reducing costs, decreasing undesirable wastage of resources, limiting offsite interactions, and having explicit and increased effects (Prasad et al. 2017). In agriculture, this pertains to significantly reducing the application of chemicals, instead employing a smarter delivery mode of active ingredients facilitating better and efficient essential resource (water, nutrients, etc.) management (Zhao et al. 2018). A more exciting and enticing application prospect of nanotechnology is in the field of plant breeding and genetic transformation (Elemike et al. 2019; Cunningham et al. 2018).

Genetic improvements of crops generally involve the cellular level diversion of genes to a desired location for target gene expression, which could be for a variety of purposes like imparting resistance to pest(s), tolerance to climatic anomalies or to induce additional productivity traits. These genetic alterations are intended for improving the overall quality of crops (Abdallah et al. 2015). A general routine of two distinct steps are followed during genetic engineering of plants: (1) transient transformation—the introduction of desired DNA into plant cells, and (2) stable transformation—subsequent integration of foreign DNA with plant genome. Though each step poses its own challenges, the proper integration of the transgene into the host genome is the most crucial part to produce transgenic plants with desired traits (Bates et al. 1990). This process of transformation is generally conducted under the protective environment of sterile laboratory conditions and engineered plants need to regenerate from transformed tissues which again introduces newer challenges.

Introduction or transfer of genes has been conventionally achieved by (1) natural method—using natural agents as *Agrobacterium* species, viruses, etc., (2) direct method—protoplast fusion, transfection, etc., (3) physical method—electroporation, particle bombardment, microinjection, etc., and (4) chemical method—gene transfer using plasma membrane destabilizing/precipitating agents as PEG, PVA, $NaNO_3$, DEAE, dextran, DMSO, etc. (Demirer and Landry 2017). Although successful, these conventional methods were plagued with limited transformation rates due to various reasons, the most prominent being utilization of excessive energy and chemicals inflicting damage to DNA and cells. Circumventing these issues would result in an efficient process and a more productive outcome.

Nanotechnology-based processes promise effective solutions for such limitations. Various nanocarriers such as liposomes, polymeric and inorganic nanoparticles (NPs), carbon nanotubes (CNTs), and quantum dots (QDs) have been successfully tested for their abilities to carry genes of interest to the desired host system with commendable success rates (Cunningham et al. 2018). This chapter will dwell into the implications (past, present, and future) of nanotechnological interventions in the field of plant genetic engineering while comparing the conventional modules as well.

1.2 Conventional Plant Biotransformation Techniques

Methods for plant biotransformation have been adapting to the various advancements in time to achieve better and stable gene expression outcomes. Though technological advancements have been implemented, conventional gene delivery approaches are still being used (Cardi et al. 2017). These conventional methodologies fall under three predominant classes: physical (biolistic particle bombardment/gene gun, electroporation—using electric field pulses to create pores in cell membranes and microinjection), chemical (PEG-mediated), or biological (Agrobacterium-mediated) with their own advantages and limitations specific to the mode of application (Table 1.1). Yet, the limitations outweigh the advantages and hence the need for promising alternatives. Nanotechnological interventions that are being developed to circumvent these limitations of conventional approaches and simultaneously enhancing overall process efficiency are discussed in this chapter.

1.3 Why Nanotechnology?

With conventional plant gene delivery methods facing serious issues, prospective alternatives that are cost-effective, easy, robust, non-toxic, and that can transfer genes into all phenotypes irrespective of the species become a necessity. Nanotechnology promises augmentation of agricultural productivity by highly specific and reliable genetic transformation methods at the cellular level (Sekhon 2014).

The nano-approach advertises numerous advantages over the conventional practices, with regards to its ease of operation and high efficiency (Mishra et al.

Table 1.1 Conventional gene delivery methods, advantages, and drawbacks

Conventional gene delivery methods		Advantages	Drawbacks
Physical methods	Biolistics (gene gun)	• Facile process • Large size/quantity of DNA transfer possible	• Compromised DNA integrity • Poor efficiency and short life span of expression • Damage to host
	Electroporation	• Rapid • Cost-effective	• Limited to certain plant species • Compromised DNA integrity • Damage to host
	Microinjection	• Direct injection into plant protoplasts or cells • Suitable for use in large cells • Effective and easy gene transfer to the nucleus • Direct introduction of gene by penetrating the cell membrane	• Not suitable for small cells or tissues. • Infrequent gene transfer method in plant biotransformation • Low efficiency
Chemical methods	PEG-mediated	• High-efficiency protoplast transfection	• Highly restricted protoplast regeneration into whole and fertile plants
Biological methods	Agrobacterium-mediated	• Cost-effective • High efficiency • Stable transformation	• Limited to certain plant species
	Virus-mediated	• Useful for transient and whole-plant expression • Independent of host range limitation	• Non-selectivity • Slow process • Low DNA size carrying capacity

2017). For example, a thousand times less amount of DNA is required for the detection of expression than the conventional methods. Transient DNA-free genome editing (including gene silencing) is enabled in a controlled fashion. Co-delivery of multiple biomolecules (DNA activator, DNA proteins, different genes), simultaneously to the target, is facilitated. The surface of the gene nanocarriers can be easily functionalized using certain bio-recognition entities for specific, targeted delivery. The non-toxic nature of nanocarriers and their local translocation to individual cells, organs, or tissues is an additional advantage.

Particles with size ranging from 1 to 1000 nm are regarded as nanoparticles or nanocarriers (Nair et al. 2010, 2012). The distinctive small size and unique surface properties project them as versatile carriers for genes and other biomolecules. NP-based biotransformation proposes numerous benefits: (i) faster gene transfer than Agrobacterium-based process, (ii) DNA encapsulated in protective layers therefore resistant to damage/inactivation, (iii) gene mutation due to energy-induced DNA damage (typically in physical methods) is greatly reduced, (iv) greater control over transformation process, and (v) amalgamation of nano- and physical methods is possible leading to effective and improved gene transfer. So far, a wide range of nanomaterials such as liposomes, CNTs, QDs, and silica NPs have been used for plant gene engineering (Nair et al. 2010).

In contrast to the animal system where the application of nanotechnology for gene delivery has been widely demonstrated, in plants, owing to the presence of a rigid cell wall which restricts the transport of molecules into plant cells, research has been slightly sparse (Rai et al. 2012). NPs have interesting value as intracellular biomolecule delivery materials, such as (i) their biological membranes trespassing ability, (ii) ability to carry, shield and release various payloads, and (iii) attain specific targeting by facile surface modification (Sokolova and Epple 2008). The NP-based gene delivery in plants is limited not only by the cell wall but also by the general in vitro plant studies. The regeneration capacity in in vitro cultures varies greatly across species, genotype, and even in individual plant depending on the developmental age of source tissue. As of now, regardless of the delivery method, all stable transformations need progeny regeneration from embryogenic calli. Therefore, delivery and regeneration optimizations are essential for improving the efficiency of stable transformation across a wide range of plant species.

1.4 Nanocarriers for Plant Biotransformation

NPs for the delivery of biomolecules (nucleotides, activators, proteins) to plants in vitro and in vivo (Mohamed and Kumar 2016a) are being explored at a much-enhanced pace than ever before. NP-mediated genome editing to deliver green fluorescent protein (GFP) gene-containing plasmid and functional recombinase into plant tissues has been a great success. One prominent example is that of mesoporous silica NPs (MSNs) for delivery of DNA and its activator into tobacco plant via isolated cells and intact leaves (Torney et al. 2007). Furthermore, MSNs, single-/multi-walled CNTs (SWCNTs/MWCNTs), gold NPs (AuNPs), magnetic virus-like NPs (MVNPs), carbon-coated magnetic NPs, QDs, and starch NPs have been employed in this regard (Mohamed and Kumar 2016b; Nair et al. 2012).

1.4.1 Silica Nanoparticles

Looking at a few detailed examples, MSNs-DNA complex was delivered into intact roots of *Arabidopsis thaliana* without any involvement of mechanical force

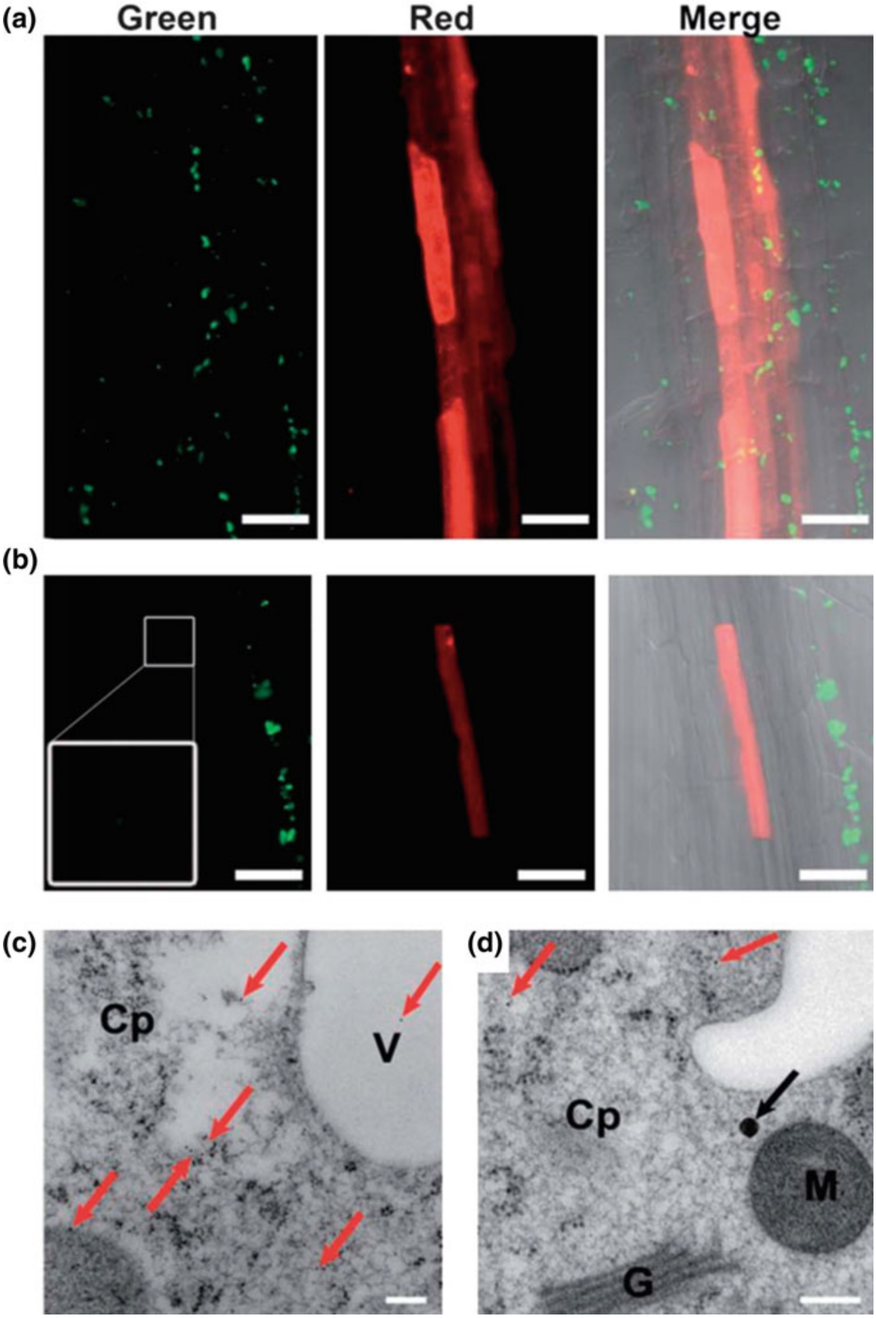
(Chang et al. 2013). Fluorescence labeling along with antibody detection was used to confirm the gene expression from the epidermal and inner cortical and endodermal (not possible with conventional physical methods) root tissues. Simple co-culture was enough for MSNs to infiltrate the cell wall resulting in transient gene expression in intact Arabidopsis roots, thereby negating the need for physical injury causing conventional biolistic approaches (Fig. 1.1).

Biolistics mediated co-delivery of AuNP functionalized MSNs (Au-MSN), with large average pore diameters (10 nm) and fluorescently labeled protein, bovine serum albumin (BSA) along with plasmid DNA, an enhanced green fluorescent protein (eGFP) into *Allium sativum* (onion) plant tissues was reported (Ortigosa et al. 2012). A proof-of-concept experiment demonstrated Au-MSN delivery and release of proteins and plasmid DNA in the same cell after trespassing the cell wall via biolistic approach. This was the first example of co-delivery of active non-denatured proteins and plasmid DNA (eGFP fluorescence) to plant cells providing new insights into NP-mediated cargo delivery to plants.

Genome editing can be carried out without direct delivery of DNA as such, rather with proteins or enzymes that can initiate/facilitate biochemical analysis or genome modifications. This can negate DNA (transgene)-genome integration and result in precisely modified "non-transgenic" plants. In this regard, gold-plated MSNs-protein (Cre recombinase) complex were used to deliver the protein via biolistics into *Zea mays* (maize) cells harboring loxP sites flanking a selection gene and a reporter gene (Ortigosa et al. 2014). With the release of Cre protein from MSNs, recombination of loxP sites followed by elimination of both genes occurred. Fertile plants were regenerated from selected recombination events with nearly 20% of embryos developing calli with recombined loxP sites. This technology is a DNA-free module for genome editing where MSNs can be modified to accommodate specific enzymes and target desired tissue.

Torney and co-workers utilized honey-comb-like MSNs to transport DNA and chemicals into *Nicotiana tabacum* via biolistics (Torney et al. 2007). MSNs were loaded with the gene and its inducer, and to further prevent unwanted escape from MSN pores, the ends were capped with AuNPs through disulfide bonds. The significance of disulfide bonds is in cellular environments, where they are reduced, resulting in the release of DNA, conditions which can be precisely controlled. Optimal DNA/MSN ratio was found to be 1:10 (w/w), wherein, a stable DNA-MSN complex was formed, without any free DNA in solution post 2 h of incubation. Transient GFP expression was observed post 36 h of DNA-MSN incubation

Fig. 1.1 MSN-mediated gene delivery. **a**, **b** Confocal microscopic images of DNA-MSN ▶ complex (1: 100 ratio) treated (48 h at 24 °C in 1/2 MS) Arabidopsis root cells. Gene expression (mCherry protein; red) was observed in endodermal (**a**) and cortical (**b**) cells. TMAPS/F-MSNs were present in cells expressing mCherry (**b**, green channel). Scale bars: 50 mm. **c**, **d** TEM of immunogold-labeled mCherry protein in root cells after incubation with DNA-MSN complexes. Red arrows show the gold-labeled mCherry proteins. Presence of TMAPS/F-MSNs (black arrow) and mCherry protein (red arrows) in the same cell (**d**). Scale bars are 200 nm. Cp, cytoplasm; M, mitochondrion; V, vacuole; G, Golgi apparatus. Reproduced with permission from RSC


(a)
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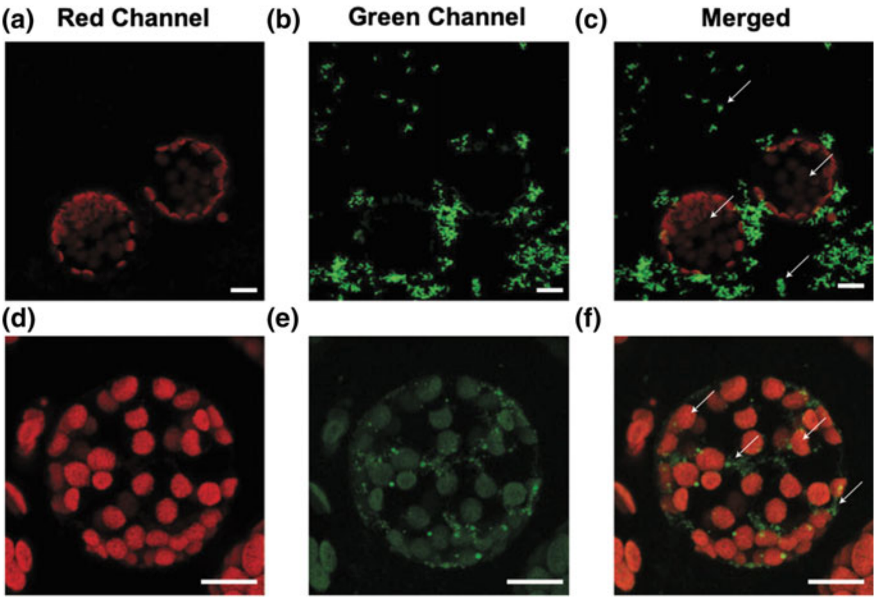
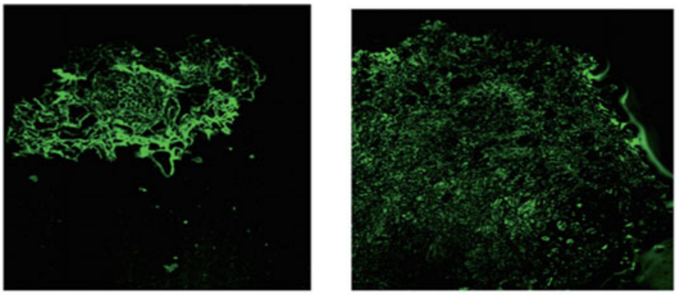


Fig. 1.2 Confocal imaging of MSN uptake by tobacco mesophyll protoplasts. Protoplasts incubated with **a**–**c**, type-I MSNs (single focal plane images) and **d**–**f**, type-II MSNs (three-dimensional reconstruction images). No uptake of type-I MSNs was observed, but type-II MSNs were internalized. Both MSNs are functionalized with fluorescein and visible in green (thick arrows). Auto-fluorescing chloroplasts in the protoplasts are in red (thin arrows). Reproduced with permission from NPG

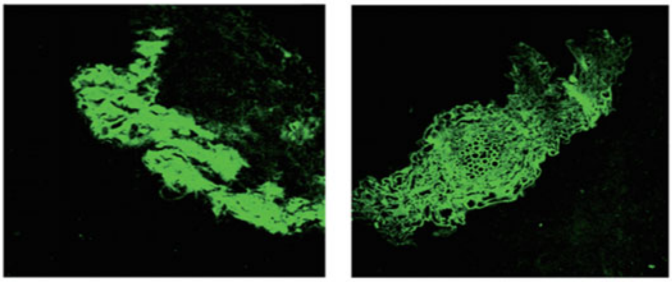
(Fig. 1.2). This stable nanoconstruct can be utilized for genetic transformation of plants or to induce pathogen-activated defense response.

1.4.2 Calcium-Based Nanoparticles

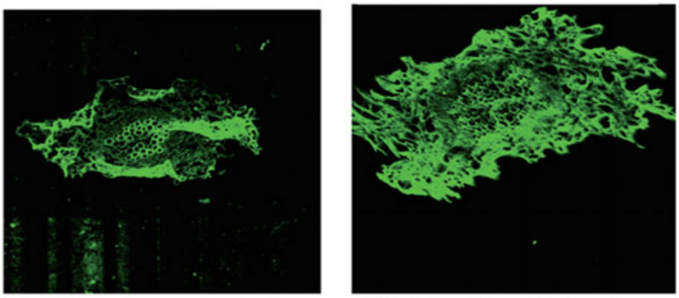
In another work, 20–50 nm calcium phosphate (CaP) NPs carrying a reporter gene (pCAMBIA1301) was employed (Naqvi et al. 2012). Gel electrophoresis was used to determine pCAMBIA1301 encapsulation and pH-dependent dissolution of CaPNPs. The encapsulation of DNA in CaPNPs was highly beneficial in protecting it from intracellular nucleases. A transformation efficiency of 80.7% was achieved with the nanocarrier when compared to *Agrobacterium tumefaciens* (54.4%) and naked DNA (only 8%), clearly highlighting the superiority of the NP-mediated genetic transformation over the conventional module. The authors suggest the release of plasmid DNA from CaPNPs in the cell, perhaps facilitating nuclear entry as opposed to the case of *A. tumefaciens* infection where transgenic GUS (b-glucuronidase) integrates into genomic DNA by non-homologous recombination. Also, this nanoconstruct did not cause any injury to the plant cell while delivery (Fig. 1.3).



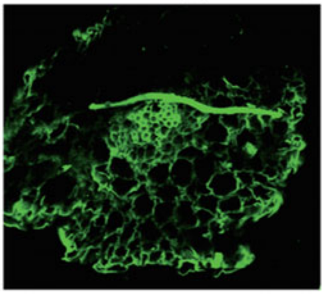
(a) 5 min incubation time (b) 4 hrs incubation time



(c) 8 hrs incubation time (d) 12 hrs incubation time



(e) 16 hrs incubation time (f) 20 hrs incubation time



(g) 24 hrs incubation time

Fig. 1.3 Confocal scanning laser microscopy of FITC–dextran loaded CaP nanoparticles incubated with hypocotyl section of *Brassica juncea* L. cv. Pusa Jaikisan at different time intervals, i.e., **a** 5 min, **b** 4 h, **c** 8 h, **d** 12 h, **e** 16 h, **f** 20 h, and **g** 24 h. Reproduced with permission from RSC

In a similar kind of work, some researchers developed CaPNPs (25–55 nm) and successfully delivered pBI121 harboring GFP driven by 35S promoter-encoding plasmid DNA in tobacco plants (Roy et al. 2003). Due to pDNA being anionic, easy encapsulation into CaPNPs was achieved. The pBI121 with GFP-loaded CaPNPs was an alternative non-viral vector for easy and efficient gene delivery while providing protection from cellular nuclease enzymes.

It is known that gene encapsulation into biocompatible carriers augments the biotransformation process and provides protection to the gene, cell, and enzymes. Genetic manipulation of *Cichorium intybus* L. with CaPNPs loaded with pBinAR containing trans-*hmgr* gene was performed (Rafsanjani et al. 2016). A transformation efficiency of 9.6% was recorded, with the transgenic plants showing higher levels of chlorophyll, soluble protein and esculin, attributed to the higher expression of *hmgr* transgene and increased activity of HMGR enzyme. These nanoparticles could be useful in producing genetically engineered plants of desired and enhanced traits.

1.4.3 Magnetic Nanoparticles

Magnetic gold nanoparticles (mGNPs) covalently bound to fluorescein isothiocyanate (FITC) molecules were delivered into *Brassica juncea* (canola) cells with/without cell walls under an external magnetic field (Hao et al. 2013). The translocation of NPs was confirmed from sectional transmission electron microscopy (TEM) images and further by confocal images where green fluorescence in the protoplasts and walled cells was observed, with a delivery efficiency of 95%. Further, canola cells with/without cell walls were targeted with plasmids-mGNPs complex. Post 48 h culture, blue color (X-Gluc) developed in the protoplasts, indicating the expression of the GUS gene. Meanwhile, intact cells (with cell wall) exhibited a green color, possibly a mix of blue and yellow from the suspension cells themselves. The positive gene expression and non-cytotoxic nature of mGNPs even with the toxic dye FITC, project this nanocarrier as an efficient gene and biomolecule delivery vector.

It is a fact that majority of the genetic modification modules depend on tissue regeneration from culture, often associated with long and arduous processes. In addition, certain crop species pose difficulty in regeneration, for example, cotton. Therefore, a novel transformation technique, pollen magnetofection, was developed for the direct production of transgenic seeds, bypassing regeneration (Zhao et al. 2017). Herein, exogenous DNA-loaded magnetic nanoparticles (MNPs) were directly delivered into pollen under a magnetic field. These magnetofected pollen were utilized for pollination, resulting in transgenic plants from transformed seeds. The successful integration of exogenous DNA into the genome was expressed and inherited in the offspring. The advantages of such a system are that it does not require laborious culture procedures and is genotype independent. Additionally, it is a facile and rapid process with multi-gene transformation capabilities and suitable for almost all crops, with an imminent impact in developing new varieties of transgenic crops.

1.4.4 Dendrimers

Cationic polyamidoamine (PAMAM) dendrimers are nanoparticles with a tunable number of branches and unique molecular features, making them one of the most promising nanocarriers for gene delivery applications. A diethylenetriamine core hyperbranched PAMAM (hPAMAM)-G2 dendrimer was used to conjugate with DNA (ssDNA-FITC-hPAMAM) and tested with delivery to alfalfa cells. Additionally, the efficacy of ultrasound (US)-mediated delivery of hPAMAM-G2 and gene expression (gusA) was probed (Amani et al. 2018). The electrophoresis retardation analysis (DNA-dendriplex dissociation) portrayed partial DNA protection from sonication damage with N/P ratios (where N is the number of nitrogen atoms in dendrimer and P is the number of phosphorus atoms in DNA) < 2 and with better DNA protection corresponding to increasing N/P ratios. Sonication increased the ssDNA delivery by 36%, significantly higher than without sonication group. Also, the N/P ratio was essential in determining the efficiency of transfection and gusA gene expression with the highest efficiency (1.4%) recorded at an N/P ratio of 10. The US (120s) and hPAMAM–DNA combination proved to be optimal with the highest gusA gene transfection and expression of 3.86%.

A similar work involving supramolecular complexes of G4 poly(amidoamine) dendrimers with GFP-encoding plasmid DNA via electrostatic interaction, to *Agrostis stolonifera* L. (creeping bentgrass) was reported. The fluorescently (TRITC) labeled dendrimers were recorded to enter the cells of turfgrass and expressing the GFP gene in the plant cells as observed by confocal fluorescence microscopy. It was concluded that the efficiency of transfection might be further enhanced with optimization of conditions as cell culture media pH and the molar ratio (N/P) of dendrimer/DNA (Pasupathy et al. 2008).

1.4.5 Liposomes

Liposomes are fascinating particles which bear a close resemblance to the plasma membrane of cells, mostly synthesized by components found inside the living system, thereby rendering them high biocompatibility. Their flexibility and ability to carry large payloads garner them unprecedented scientific appreciation. Deshayes et al. developed negatively charged liposomes encapsulating an *Escherichia coli* plasmid, pLGV23neo, carrying a kanamycin resistance gene (Deshayes et al. 1985). PEG was used to facilitate the fusion of liposomes with tobacco mesophyll protoplasts. Kanamycin-resistant clones were isolated from transfected cultures at an average frequency of 4×10^{-5} with the leaf protoplasts being resistant to kanamycin at 100 µg/mL. Aminoglycoside 3′-phosphotransferase II, a pLGV23neo encoded enzyme, was detected in the leaf extracts. At least one of the transformants had approximate 3–5 copies of the kanamycin resistance encoding genes inserted in their genome, making the experiment a commendable success.

In another work, Caboche and co-workers prepared unilamellar liposomal vesicles encapsulating pUC8CaMVCAT plasmid vector with the CAT gene (chloramphenicol acetyl transferase) and successfully introduced the gene in tobacco protoplasts (Caboche and Lurquin 1987). Ballas et al. synthesized tobacco mosaic virus RNA (TMV RNA)encapsulated liposomes (formulation of phosphatidylcholine/cholesterol) (Ballas et al. 1988). The surface of the so-developed liposomes was functionalized by quaternary ammonium detergent, di-isobutyl cresoxyethoxyethyl dimethyl benzylammonium (DEBDA [OH–]), thereby introducing surface hydroxyl groups which facilitated efficient TMV RNA transfer into tobacco and petunia protoplasts, within 48 h.

Wiesman et al. synthesized liposomes utilizing vernonia oil (a natural epoxidized triglyceride)-derived cationic amphiphilic compounds for DNA encapsulation (Wiesman et al. 2007). Sawahel utilized lipofectin for effective transfusion of *N. tabacum* and *N. plumbaginifolia* mesophyll protoplasts (Sawahel 2002). During their experiments, they confirmed that the CaMV-35S promoter controlled ß-glucuronidase gene had lower transformation efficacy than the PEG-mediated method.

1.4.6 Gold Nanoparticles

Due to their unique properties at the nanoscale, gold nanoparticles have found extensive applications in sensors and other biomedical applications. Though their use in plant biotransformation has been limited, it is on a steady rise. AuNPs-embedded carbon matrices were synthesized by heat treatment of the intracellular biogenic AuNPs produced by the fungus *Aspergillus ochraceus*. Vijayakumar and co-workers utilized these AuNPs (5–25 nm) for the successful delivery of plasmid DNA into *N. tabacum* utilizing gene gun (Vijayakumar et al. 2010). A similar DNA delivery demonstration was conducted in the same work with *Oryza sativa* (a monocot) and *Leucaena leucocephala* (a hard dicot tree species) with negligible cellular damage. Compared with conventional gene gun approaches using micrometer Au particles, it was established that the small size of AuNPs assists in easy and efficient embedding in the matrices which in turn enhances the transformation efficiency. On the other hand, less raw material (gold and plasmid) is needed to achieve the same level of transformation efficiency, aided by lower toxicity levels as well.

DNA-coated AuNPs were used for stable transformation of commercially important cultivars of *Glycine max* L. (soybean) callus. Soybean embryos (immature) were targeted with highly accelerated DNA-NP complex. Subsequent protoplast cultures were initiated under controlled conditions for the introduced neomycin phosphotransferase II gene. Kanamycin-resistant calli were obtained from the transfected cultures. Foreign gene expression was confirmed with enzyme assays and Southern blot hybridization (Christou et al. 1988).

1.4.7 Carbon Nanotubes

Liu et al. (2009) were supposedly the first to exploit CNTs for delivery of genes to plants. The independent (externally unaided) cellular uptake of both SWCNT/FITC and SWCNT/ssDNA-FITC conjugates was demonstrated in *N. tabacum* cells, validating the CNTs ability to penetrate intact plant cell walls and cell membranes (Liu et al. 2009). Later, Giraldo et al. (2014) injected the ssDNA-SWCNTs into the underside of *A. thaliana* leaves, using a syringe. They found that certain CNTs (defined size and charge) penetrated cell membranes without any external assistance (gene gun). The near-infrared (NIR) fluorescence emission of SWCNTs was used to understand their transport and localization in plant cells. Leaf tissue cross sections revealed the localization of ssDNA-SWCNTs in the leaf lamina and veins in intra- and extracellular parenchyma tissues and in chloroplasts (Fig. 1.4). These observations were depictive of successful trespassing of the plant cell wall, cell membrane, as well as the chloroplast membrane. Curiously, the leaf life span and chlorophyll content seemed to be unaffected by the infiltrated ssDNA-SWCNT solution, an assurance of non-cytotoxic nature of the complex (Giraldo et al. 2014).

Demirer and co-workers recently utilized covalently functionalized or pristine SWCNTs and MWCNTs for an efficient DNA delivery and robust transient protein expression in mature *Eruca sativa* (arugula) leaves. In the same study, cell wall-free arugula protoplasts were used for CNT-based transient protein expression, with a transformation efficiency of 85%. Again, in the same study a remarkable 95% gene (GFP) silencing efficiency was recorded for CNT scaffold-siRNA complex in *N. benthamiana* plant cell cytosol. The group was the first to demonstrate the efficient transient gene expression and silencing in mature plants by the use of CNT-biomolecules complexes. The results could spur high-throughput plant genetic transformation applications. The same group developed an efficient diffusion-based delivery of biomolecules with pristine/chemically functionalized SWCNTs and MWCNTs into tissues/organs of intact plants of several species. In *N. benthamiana* (Nb), *E. sativa* (arugula), *Triticum aestivum* (wheat), and *Gossypium hirsutum* (cotton), efficient delivery of DNA followed by robust protein expression (devoid of transgene integration) was achieved. Additionally, a gene silencing efficiency of 95% was observed with small interfering RNA (siRNA) delivery to Nb leaves. Here again, the nanomaterials apart from ferrying biomolecules into plant cells were able to safeguard polynucleotides from nuclease degradation. The results encourage species-independent, passive delivery of biomolecules, devoid of transgene integration, for various biotechnological applications (Demirer et al. 2019).

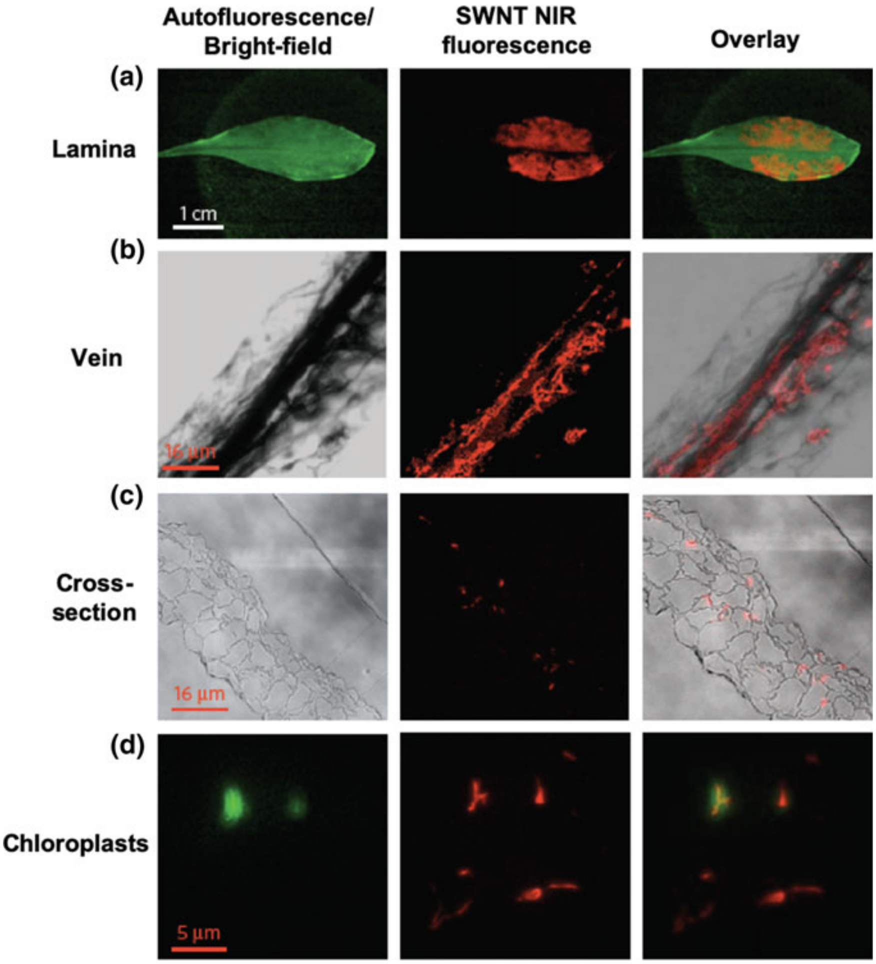


Fig. 1.4 Nanoparticle transport inside isolated chloroplasts and leaves. **a** CRi Maestro images of ss(AT)15–SWNTs within the leaf lamina of *A. thaliana*. **b**–**d**, Co-localization of ss(AT)15–SWNTs near leaf veins (**b**), in parenchyma cells (**c**), and chloroplasts in vivo (**d**). Reproduced with permission from NPG

1.4.8 Other Nanoparticles

ZnS nanoparticles (3–5 nm) modified with positively charged poly-L-lysine were utilized for transformation of tobacco cells by delivering GUS-encoding plasmid DNA (pBI121), assisted by ultrasound (Fu et al. 2012). Molecular analysis as polymerase chain reaction (PCR), Southern blot, and GUS histochemical staining was performed on regenerated plants. Higher transformation efficiencies (43.42, 48.57, and 52.67%) were recorded with ZnS NPs-DNA complex as compared to conventional US-based transformation route (30–40%). This is primarily attributed to the shielding effect provided to the DNA by ZnS NPs. The stable expression results by ZnS NPs demonstrate their role as gene protector and carriers (Fu et al. 2012).

Quantum dots have been widely used as fluorescent bio labels in in vitro cell and in vivo animal imaging studies and off late for theranostics (therapy and diagnostic) as well (Mohamed et al. 2016). In plant sciences, QDs are mainly utilized for tracking the fate of NPs-DNA complexes during/post cell transfection and subsequently in plant transformation. Water-soluble CdSe QDs were synthesized for labeling chitosan-DNA NPs via electrostatic interaction. This CdSe-chitosan-DNA complex was utilized for the genetic transformation of *Jatropha curcas* cells. Full-length PCR amplification of the reporter gene (GFP) revealed that the DNA was not degraded in *J. curcas* cells transfected with the nanocomplex rather the target DNA was integrated into the plant genome as evidenced with fluorescence detection of the complex in the transformed calli (Wang et al. 2011).

Virus resistance in plants can be imparted by the topical application of pathogen-specific double-stranded RNA (dsRNA), an attractive alternative to transgenic RNA interference (RNAi). However, spraying naked dsRNA onto plants exposes its instability, thereby limiting practical application. Mitter et al. loaded dsRNA in layered double hydroxide (LDH) clay nanosheets which were non-toxic as well as biodegradable. The advantages of such a carrier include stable and robust dsRNA loading that does not wash off, presents sustained release from the nanocarrier and can be detected even after 30 days of application from sprayed leaves. LDH degradation, dsRNA uptake by cells, and homologous RNA silencing were recorded (Fig. 1.5). On comparison of sprayed and newly emerged unsprayed leaves, a single spray of dsRNA-LDH complex proved to provide effective virus protection for at least 20 days. The results witnessed in this work translate to the near future development of RNAi-nanosprays for a diverse range of applications (Mitter et al. 2017).

Starch, owing to its biocompatible and biodegradable nature, has been studied in the nanoform for gene delivery applications. The starch NPs-gene complex was efficient enough to cross the cell wall, via US-assisted induction of transient pores in the cell wall, cell/nuclear membrane. Working in the same area, Liu and co-workers synthesized poly-L-lysine coated starch NPs (50–100 nm) in water oil microemulsion and surface modified with fluorescent $[Ru(bpy)_3]^{2+}\cdot 6H_2O$ conjugated to pEGAD plasmid DNA. They demonstrate the DNA protective effects of starch NPs in the DNA-NP complex from US damage and DNase I cleavage in plant suspension cells of *Dioscorea zingiberensis*. It was concluded that starch NPs could successfully be used in plant transformation as efficient nanocarriers of nucleic acids, assisted by US (Liu 2008).

Apart from improving yield, imparting disease resistance via gene transformation is also an essential aspect of sustainable agriculture. Chitosan NPs were encapsulated with thionin genes (AT1G12660 and AT1G12663) from *Arabidopsis thaliana*, in pEGAD vector and delivered to potato plants (Abdel-Razik et al. 2017). Thionin is an antifungal protein with action against pathogenic fungi of potato as

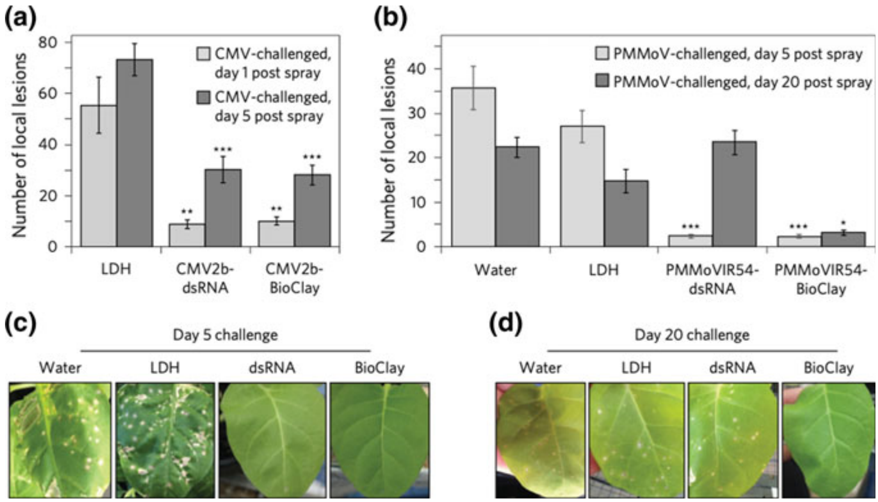


Fig. 1.5 BioClay (dsRNA-LDH) spray provides protection against viruses in local lesion assays. **a** Local lesions caused by CMV inoculation on cowpea. Plants at the two-leaf stage were sprayed with LDH, CMV2b-dsRNA, and CMV2b-BioClay on day 0 (n = 8–16 leaves per treatment group). Plants were mechanically inoculated with CMV at 1- or 5-day post-treatment. Lesions were counted 10 days post viral challenge (pvc). **b** Local lesions caused by PMMoV inoculation on N. tabacum cv. Xanthi. Plants were sprayed with either water, LDH, PMMoVIR54-dsRNA, or PMMoVIR54-BioClay on day 0 (n = 10–25 leaves per treatment group). Plants were mechanically inoculated with PMMoV at either 5- or 20-day post-treatment and necrotic lesions were counted 10 days pvc. **c**, **d** Images are showing the extent of necrotic lesions on N. tabacum cv. Xanthi leaves challenged with PMMoV 5-day post-spray treatment (**c**), and 20-day post-spray treatment (**d**). $*P < 0.05$, $**P < 0.01$ and $***P < 0.001$ are significant using the Kruskal–Wallis test with post-hoc Nemenyi test for multiple comparisons between samples compared with LDH. Data represent mean ± s.e.m. Reproduced with permission from NPG

Alternaria alternata and *Rhizoctonia solani*. Two prominent potato cultivars (lady and spunta) were chosen for transformation studies. RT-PCR was used for confirmation of thionin transgene expression in transgenic plants. Two assays were performed on transgenic potatoes to test resistance to the pathogenic fungi, (i) spore suspension effect on potato organs and (ii) effect of thionin on spore germination inhibition. New transgenic cultivars were highly resistant to the fungal infection symptoms as compared to non-transgenic normal plants. These chitosan NPs-DNA complex can be an effective tool to augment disease/pest resistance in various crop species.

While further extensive research is required to fine-tune the properties and functionalization of nanoparticles, the current scenario seems promising for aggressive application of NP delivery platforms for biomolecules to plants, addressing the limitations of traditional methodologies. Biomolecular delivery to plants is marred with limitations as low gene-editing efficiency, tissue/organ damage, species limitations, cargo limitations, etc. As compared with traditional modules, NP-based biomolecule delivery promises higher-throughput plant genome editing via DNA, single-guide RNA (sgRNA), and RNP delivery, thus opening new avenues for exploration in this exciting field.

Plants have remained elusive to the advances of technology in genetic transformation techniques, especially due to the rigid cell wall hindering the delivery of essential gene modification capable cargo to mature plants. This curiously reveals a vast scope for potential in designing much more efficient nanocarriers with distinct cargo (nucleic acids, proteins) ferrying capabilities and optimal physicochemical features for efficient and independent bypass of the inherent barriers in intricate plant tissues.

1.5 Patented Technologies

Though limited, there has been a rise in patent applications in the field of nanocarrier-based biomolecule delivery to plants, especially with regard to enhancing specific traits of desired plants via transformation. Recent patents 20110065092A1 (gene-encapsulated non-viral particle) and US6534484 (gene-encapsulated liposome for biotransformation) highlight the importance and necessity of nanotechnology in biotransformation. Few more patents assigned to nanotechnology-based biotransformation are enlisted in Table 1.2.

1.6 Concluding Remarks and Future Perspectives

Engineering of plants at the gene level has impacted the global society in an unimaginable manner and has accelerated scientific ingenuity to develop crop variants with enhanced features as resistance to pests and diseases, tolerance to stress (abiotic/biotic), and enrichment of nutritional values. Advanced site-specific genome editing technologies have fine-tuned the precision with which genetic augmentation of plants is accomplished. Conventional approaches are greatly limited by the presence of the rigid cell wall, which makes penetration of biomolecules near to impossible without significant damage or loss of action. Agrobacterium has been the most revered plant genetic transformation tool but has limited host species range and is consistently under regulatory oversight in many countries. Biolistic and PEG transfection, though boast some perks over their biological counterpart, face severe difficulties in healthy plant regeneration from transformed tissues with low-editing efficiency. NPs are now established in in vitro mammalian cultures with a large population finding its way to human trials and further clinical applications. On the other hand, they are still in infancy when it comes to application in plants with much scope for investigations in future plant biotechnology and genome engineering. Initial reports have shown the potential of properly synthesized and functionalized analogues that can deliver biomolecules to

Table 1.2 Few nanoparticle-based patents on plant biotransformation

Patent title	Patent number	Invention
Plant delivery inventions		
T-DNA/protein nanocomplexes for plant transformation	US20120070900A1	DNA/protein nanocomplex for transfecting eukaryotic cells, wherein the nanocomplex comprises an expressible nucleotide molecule complexed with a VirD2 protein molecule, and a RecA protein molecule complexed with the nucleotide molecule/VirD2 protein molecule complex. The nucleotide molecule/VirD2 protein molecule/RecA protein molecule complexed may be further complexed to a cell-penetrating peptide. The DNA/protein nanocomplex can be used for delivering the expressible nucleotide molecule to target plant cells, in particular, monocot plant cells exemplified by wheat cells, corn cells, triticale cells, barley cells, and rye cells
Delivering compositions of interest to plant cells	US2011203013 (A1)	Nanoparticle–microparticle mixture can be used to provide a composition of interest to a plant or plant cell
Compositions and methods for delivery of a polynucleotide into a plant	WO2016196738A1	Compositions and methods for delivering a polynucleotide from the exterior surface of a plant or plant part into the interior of a plant cell. More specifically, the present disclosure relates to compositions comprising at least one polynucleotide and at least one agent that is able to disrupt at least one barrier of the plant or plant part
DNA-loaded supported gold nanoparticles, process for the preparation and use thereof	EP2462227A1, WO2011016053 (A1)	Relates to carbon embedded nanogold particles with sharp edges useful for gene delivery
Compositions and methods for safe delivery of biologically active plant transformation agents using non-fibrous silicon carbide powder	WO2007050715A2	A biologically active nucleic acid may be directly delivered into plant cells in an improved and operator-safe fashion using encapsulated or complexed nucleic acid formed into nanoparticles, using

(continued)

Table 1.2 (continued)

Patent title	Patent number	Invention
		carborundum powder, a nucleic acid-binding protein with nuclear localization signals (NLSs), or both
Other general inventions extendable to plant gene delivery		
Transfection reagents	US7915450B2	Cationic lipids and their compositions for macromolecule delivery to cells
Use of non-viable particles comprising an internal control (IC) nucleic acid	US20110065092A1	Non-viable particles (particularly liposomes, particles made of viral protein coat or synthetic polymers, non-viable genetically modified organisms), comprising an IC nucleic acid sequence in nucleic acid-based analysis
Lipid-encapsulated polyanionic nucleic acid	US8021686B2	Preparation of a lipid-nucleic acid composition
Method of inserting DNA into living cells	US4394448A	DNA/fragments of DNA insertion into live cells, by means of encapsulation in a lipid vesicle with subsequent contact with cells, facilitating insertion
Cationic lipids for intracellular delivery of biologically active molecules	EP0523189B1	Cationic lipids for efficiently delivering biologically active agents (drugs, proteins, polynucleotides, peptides, etc.) by assisting in transport across membranes or by promoting adhesion to biological surfaces
Lipid-nucleic acid particles prepared via a hydrophobic lipid-nucleic acid complex intermediate and use for gene transfer	US5976567A	Nucleic acid introduction into cells via lipid-nucleic acid particles
Methods for encapsulating plasmids in lipid bilayers	US6815432B2	In vitro and in vivo transfection of cells using plasmid-lipid particles

plants in vitro and in vivo with better efficiency than conventional methods, though still some of them require external aid (i.e., gene gun). Not only the nanocarriers, but the auxiliary systems such as the ultrasound and the magnetic field generation systems should also be developed to better support the nanocarriers in enhancing their inherent potentials to the extent possible. The steps to the future are happening now, with numerous researchers fully engrossed in finding the perfect nanosystem for delivering the most sensitive of biomolecules across the most rigid cell walls to achieve the best transient gene expression efficiency so far. Slow, but sure, nanotechnology with its vast trove of nanocarriers and delivery mechanisms is the hope for fighting the various agricultural issues plaguing this planet now.

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Chapter 2
Engineered Nanoparticles for Increasing Micronutrient Use Efficiency

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Abstract Micronutrients are an important class of trace elements required by both plants and animals. With increasing food demands and limited land available for agriculture, the existent agricultural practices would not be able to meet the demand of the future. Moreover, micronutrient-deficient food consumption has proven to cause long-term side effects in humans. To overcome the shortcomings of the existing technology, nanotechnology is an emerging technology with possible applications in agriculture. Nano-form micronutrients such as iron, manganese, zinc, copper, and molybdenum are being carefully analyzed for applications in crops and plants. Nanoparticles produce better results and are required in lesser amount as compared to conventional fertilizers. This chapter focuses on the effect of engineered micronutrient nanoparticles on various plants. Many studies demonstrated the growth enhancement and better functioning of plants at an optimum concentration of nanoparticles. We have further discussed the possible uptake mechanisms of these engineered nanoparticles in plants to have an insight into the mode of action of nanoparticles after entering into plant systems. To have a better understanding, it is highly desirable that we must carefully look into the negative aspects of the same. However, very few studies have taken the plant–soil system and the soil microbiota into consideration while studying the effects of nanoparticles on plant systems. Therefore, it is important that we understand the effects of nanoparticles, both positive and negative, on the plant ecosystem as a whole.

Keywords Micronutrients · Plants · Nanoparticles · Uptake · Accumulation · Toxicity

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2.1 Introduction

According to the United Nations 2017 reports, the world population in 2017 was 7.6 billion and is expected to reach 8.6 billion in 2030, 9.8 billion in 2050, and 11.2 billion in 2100 (UN 2017). The increasing population consequently leads to an increased demand for food which thus has a direct impact on agriculture. Meeting the demands of growing population calls for increasing the amount of better seeds, pesticides, fertilizers, and water (Tilman et al. 2011). Along with increased food production, nutrition-rich food is crucial to overcoming malnutrition, especially among women and children. Micronutrients are a group of elements that are required in trace amounts by the plants. These include iron (Fe), copper (Cu), zinc (Zn), manganese (Mn), molybdenum (Mo), boron (B), chloride (Cl), and nickel (Ni) (Liu and Lal 2015; Monreal et al. 2015). Micronutrient-deficient food causes anemia and reduction in height and decreases cognitive and physical performance in children. Micronutrient deficiency in childhood may have long-term effect till adulthood (Swaminathan et al. 2013). However, current techniques and methods to supply micronutrients in the soil are ineffective and have low crop fertilizer—micronutrient use efficiency (<5%) (Monreal et al. 2015). It has also been observed that the existing conventional agriculture practices would not be able to increase productivity any further (Monreal et al. 2015).

The availability of micronutrients in soils is subject to factors like pH, soil organic matter (SOM), clay content, redox potential, biological activity, and cation-exchange capacity (Fageria et al. 2002). Presumably, micronutrient nano-fertilizers may enhance the bioavailability of these nutrients to plants even under these worst-case scenarios. Since development and application of nano-fertilizers are still at initial stages, there are few researches or systemic studies on the effects and advantages of applying micronutrient in form of nano-fertilizers under field conditions. This has the potential to become efficient and cost-effective tool to meet the increasing food demands and to fight food shortage and micronutrient deficiency.

This chapter covers the positive and negative effects of different micronutrient nanomaterials on the plants. Further, to get a better idea of the transport of nanomaterials, the studies pertaining to the uptake mechanisms and accumulation of various nanoparticles in different plants have been discussed. Since plants are an important and integral part of the ecological system, there is a need of better understanding of the interactions between the nanomaterials and plants, soil organisms, and the ecological system before implementing the use of nanoparticles on large scales.

2.2 Nanoparticles as Micronutrients

2.2.1 Iron (Fe) NPs

Iron is an important micronutrient for crop growth and is involved in chlorophyll and hormone production (such as gibberellic acid, ethylene), photosynthesis, ROS production and scavenging, mitochondrial respiration, and osmoprotection (Hänsch and Mendel 2009). Apart from this, iron plays an important role in enzymes related to energy transfer, nitrogen fixation, lignin fixation, and pathogen defense (Janmohammadi et al. 2016). Iron deficiency affects the growth, functioning, and development of the plants and also causes anemia in animals and humans (Murgia et al. 2012). Therefore, it is important to develop efficient and non-toxic and economical fertilizers to solve iron deficiency for agricultural use. For optimal growth, most plants generally require 1–5 mg/L Fe in soil solution (Hoagland and Arnon 1950). Iron deficiency is a prevalent problem in alkali soils of semiarid regions and soils with low organic matter (Fahad et al. 2014). To correct this, foliar spray in such areas is a viable option (Boorboori et al. 2018; Galavi et al. 2012).

Iron nanoparticles (Fe NPs) have been studied to show dual effects on plants: Low concentrations showed positive effects on the growth and development of plants, whereas high concentrations resulted in harmful effects on plants (El-Temsah and Joner 2012; Kim et al. 2014). It has been found that Fe NPs promote nutrient absorption and enhance the photosynthetic efficiency in plants (Scrinis and Lyons 2007; Sekhon 2014). Ghafariyan et al. (2013) studied the effect of magnetite NPs on soybean, and it was reported that low concentrations of NPs significantly increased the chlorophyll contents in subapical leaves of soybeans under hydroponic conditions. Effects of iron nanoparticles have been studied in a wide range of plants like corn, rice, maize, watermelon, and rapeseed and have been summarized in Table 2.1.

2.2.2 Manganese (Mn) NPs

Mn is required in trace amounts by plants, where it is involved in photosynthesis, respiration, nitrogen metabolism, and providing tolerance toward pathogens (Datnoff et al. 2007; Millaleo et al. 2010; Pradhan et al. 2013, 2014). The benefits of Mn applications in plants have been demonstrated in various crops like wheat, maize, beans, and soybean, where the crop yield increased several folds at required doses (Dimkpa and Bindraban 2016; Fageria 2001). Dimkpa et al. 2018 indicated that exposure to nano-Mn affects the plants in a way different to that in bulk and ionic Mn. Results suggested that the use of nano-Mn requires careful use and that foliar treatment could provide better control on plant response.

Mn nanoparticles help to enhance the functioning of the plant in various ways. Mn NPs increase the activity of electron transport chain by binding with CP43 protein chain of photosystem II (Pradhan et al. 2013). It was also reported that Mn NPs enhance oxygen evolution process and consequently improve the phosphorylation capacity (Pradhan et al. 2013). Thus, it improves the photosynthetic ability of the plants, thereby producing more sugar, and can be useful in the agricultural sector for the improvement of plant productivity (Pradhan et al. 2014). It was reported that Mn NPs are a better source of Mn as compared to commercially available bulk Mn salt and enhanced the growth and augmented in the photosynthesis of mung bean (*Vigna radiata*) (Pradhan et al. 2013). Another group

Table 2.1 Summary of the use of nanoparticles as a micronutrient

S. No.	Nutrient	Nanoparticle type and particle size	Plant	Results	Reference
1	Cu, Zn	Cu, Zn NPs	Wheat (*Triticum aestivum*)	A more positive effect of Cu and Zn NPs was seen on pro-oxidative/antioxidative balance and morphometric indexes of leaves in steppe ecotype (Acveduc) seedlings than in forest-steppe ecotype (Stolichna) under drought conditions	Taran et al. (2017)
2	Fe	Fe_2O_3 NPs (9 nm)	Soybean (*Glycine max*)	Superparamagnetic iron oxide NPs (SPIONs) significantly improved the chlorophyll content in subapical leaves of soybean	Ghafariyan et al. (2013)
3	Fe	γ-Fe_2O_3 NPs (17.7 ± 3.9 nm)	Corn (*Zea mays* L.)	No evident results for the presence of γ-Fe_2O_3 in the shoot and roots. High concentration of NPs was distributed on the surface of corn roots, which explained the cause of oxidative stress exclusively in the roots	Li et al. (2016)
4	Fe	Fe_2O_3 NPs (10 ± 3.2 nm)	Rice (*Oryza sativa* L. ssp. *indica*)	Fe content in both transgenic and non-transgenic increased with the increasing NP dose. Also, TEM images suggested that non-transgenic plant contained more Fe than transgenic line	Gui et al. (2015)
5	Fe	γ-Fe_2O_3 NPs (17.7 ± 3.9 nm)	Watermelon (*Citrullus lanatus*)	No oxidative stress on watermelon was seen at a concentration of 20 mg/L of γ-Fe_2O_3 NPs, whereas 50 and 100 mg/L of γ-Fe_2O_3 NPs caused oxidative stress on watermelon leaves but was removed later with the growth of watermelon	Wang et al. (2016d)
6	Fe	γ-Fe_2O_3 NPs (17.7 ± 3.9 nm)	Citrus (*Citrus reticulata*)	γ-Fe_2O_3 NPs could enter citrus roots, but no translocation from roots to shoots was observed. Although oxidative stress occurred in citrus plants, 20 mg/L γ-Fe_2O_3 NPs could increase chlorophyll level, while 50 and 100 mg/L of NP concentration decreased chlorophyll content. Possibly γ-Fe_2O_3 NPs at low concentration contribute to the synthesis of chlorophyll	Li et al. (2017)
7	Fe	Fe_2O_3 NPs	Watermelon (*Citrullus lanatus*)	A concentration of 20 mg/L of nano-ferric oxide was found to be appropriate dosage for watermelon to absorb and use iron from it and caused relatively lower MDA content and higher chlorophyll content	Wang et al. (2015a)

(continued)

Table 2.1 (continued)

S. No.	Nutrient	Nanoparticle type and particle size	Plant	Results	Reference
8	Fe	γ-Fe_2O_3 (~1–10 nm)	Rapeseed (*Brassica napus*)	The use of γ-Fe_2O_3 nanoparticles increased the growth rate of leaves from 33 to 50%. Also, the SPAD measurements showed increase in chlorophyll from 47 to 52%	Palmqvist et al. (2017)
9	Fe	α-Fe_2O_3 (30 nm), γ-Fe_2O_3 (20 nm), and Fe_3O_4 (20 nm) NPs	Pomelo (*Citrus maxima*)	The Fe content in plant roots on treatment with 50 mg/L of α-Fe_2O_3, γ-Fe_2O_3, and Fe_3O_4 NPs was 20.0, 25.1, and 27.5 times that of the control, respectively. On the other hand, the shoot Fe content upon exposure to 50 mg/L iron oxide NPs was like the control	Li et al. (2018)
10	Fe	γ-Fe_2O_3 NPs	Pomelo (*Citrus maxima*)	All γ-Fe_2O_3 NPs exposures showed insignificant changes as compared to the control. No oxidative stress was induced by 20 and 50 mg/L of γ-Fe_2O_3 NPs, while at high concentration (100 mg/L), γ-Fe_2O_3 NPs initially induced stress but plants were able to deal with it	Hu et al. (2017)
11	Fe	Fe_3O_4	Maize (*Zea mays* L.)	Plants treated with 54 μM of Fe in nano-form showed enhancement in plant height, biomass, and diminution in antioxidant enzyme activity as compared to the plants fertilized with Fe salt. The results indicated that nano-form Fe was more efficient than bulk Fe to increase nutrient use efficiency in crops like maize	Elanchezhian et al. (2017)
12	Fe	Fe_2O_3 (30–40 nm)	Spinach (*Spinacia oleracea*)	The experiments suggested that the use of Fe_2O_3 enhanced the growth rate of spinach in a dose- and time-dependent manner. After 45 days, the shoot length of the spinach plant grown under 100, 150, and 200 mg concentrations of Fe_2O_3 was almost 1.45, 1.91, and 2.27 times higher than that of the control spinach. The root length of spinach at 100, 150, and 200 mg of Fe_2O_3 was nearly 1.25, 1.375, and 1.75 higher than that of the control spinach	Jeyasubramanian et al. (2016)

(continued)

Table 2.1 (continued)

S. No.	Nutrient	Nanoparticle type and particle size	Plant	Results	Reference
13	Fe, Zn	FeO, ZnO NPs	Carrot (*Daucus carota*)	The best and maximum vegetative growth and yield were found in the plants treated with the combination of ZnO and FeO NP (ZnO NPs @ 100 ppm + FeO NPs @ 50 ppm)	Elizabath et al. (2017)
14	Zn	ZnO NPs (75 nm)	Cucumber (*Cucumis sativus*)	At 1000 mg/kg of ZnO NPs, shoot dry biomass decreased (52%) in the untreated soil but increased (35%) in CM (cow manure)-treated soil compared to the bulk zinc particles. Plants in the CM-treated soil showed higher concentration of zinc in their tissues than with those in untreated soil. The shoot Zn percentage for coated and uncoated NPs was 37 and 32%, respectively, which is more than that of bulk Zn (20.6%)	Moghaddasi et al. (2017)
15	Zn	ZnO (20 nm)	Mung bean (*Vigna radiata*) and chickpea (*Cicer arietinum*)	ZnO NP at 20 ppm produced the best growth results in mung seedling, i.e., 42.03% for root and 97.87% for shoot as compared to control. For gram seedlings, ZnO NP at 1 ppm caused an increase of 53.13% in roots and 6.38% in shoots. Above these concentrations, growth retardation was observed in both plants	Mahajan et al. (2011)
16	Zn	ZnO NPs	Rice (*Oryza sativa*)	Nano-form ZnO showed better results by registering an increment of 26 and 25% in fresh weight of shoot biomass and 30 and 23% for root biomass concentration of 50 and 100 ppm, respectively, as compared to bulk ZnO, while 500 and 1000 ppm ZnO nanoparticles produced unfavorable effects on growth	Singh et al. (2018)
17	Zn	Zn NP	Rice (*Oryza sativa* L.)	Zn NPs caused significant changes in radicle and plumule length and seed moisture content in the rice and showed better germination potential. It also protected rice plants from ROS damage by improving antioxidant enzyme levels	Panda (2017)
18	Zn	ZnO (30 nm)	Rice (*O. sativa*)	The results have shown that the seeds treated with 1000 ppm ZnO NPs increased the seedling vigor index (SVI), root length, and shoot length to 45.54, 22.34, and 34.88%, respectively, compared to control	Pavithra et al. (2017)

(continued)

Table 2.1 (continued)

S. No.	Nutrient	Nanoparticle type and particle size	Plant	Results	Reference
19	Zn	ZnO NPs (20–35 nm)	Tomato (*Solanum lycopersicum*)	The plant roots treated with 8 mg/L of ZnO NPs cause maximum increase of growth parameters. The same concentration also proved to be most effective in increasing carbonic anhydrase (CA) activity by 38.5% and nitrate reductase (NR) activity by 31.2%	Faizan et al. (2018)
20	Zn	ZnO (40.59 nm)	Spinach (*Spinacia oleracea*)	ZnO NPs at 125 ppm concentration increased the germination percentage to 84.75% compared to only 77.25% in control. 125 ppm ZnO also showed the best seedling length response and highest root length in the concentration of 125 ppm of ZnO NPs recorded highest root length of 29.2% over control	Lakshmi et al. (2017)
21	Zn	ZnO NPs	Corn (*Zea mays*)	The Zn concentration in roots increased from 69 to 409 mg/kg dry weight biomass by increasing the concentration of Zn NPs in soil from 100 to 800 mg/kg soil	Zhao et al. (2012b)
22	Zn and Fe	ZnO and Fe_2O_3 (20 nm)	Maize (*Z. mays*)	Fe_2O_3 and ZnO NPs caused an increase in leaf iron (22%) and zinc (11%) concentrations, respectively, when compared to the bulk form. Also, maximum value of chlorophyll a/b ratio was for Fe_2O_3 nanoparticles under 150 mM	Fathi et al. (2017)
23	Zn, Fe, and Cu	Nano-ZnO, (20 nm), nano-FeO (100 nm), and nano-ZnFeCu oxide (20–40 nm)	Mung bean (*Vigna radiata*)	Among the tested nanoparticle suspensions, the best results were recorded for ZnCuFe oxide at 50 ppm, followed by FeO at 50 ppm and ZnO at 20 ppm depending on their chemical composition, size, and surface energy	Dhoke et al. (2013)

investigated the effects of MnO_x NPs on the germination of lettuce seeds in a water medium and found that MnO_x NPs specifically improved the root elongation. However, at higher concentration of 50 mg/L, MnO_x NPs slightly reduced the germination percentage from 84% (control) to 63% (Liu et al. 2016). The rest of the studies are summarized in Tables 2.1 and 2.2.

2.2.3 Zinc (Zn) NPs

Zinc is one of the essential micronutrients required for the growth of plants and the only metal represented in all six enzyme classes—hydrolases, transferases, oxidoreductases, isomerases, ligases, and lyases (Auld 2001). Moreover, zinc is necessary for chlorophyll production, fertilization, germination, and biomass production (Estrada-Urbina et al. 2018). The effect of zinc nanoparticles has been studied in many plants with some studies recording positive effects while others showing a negative effect on plant growth. Moghaddasi et al. 2017 studied the effect of nano-zinc on cucumber in soil with and without cow dung. It found that at 1000 mg/kg of ZnO NPs, shoot dry biomass decreased (52%) in the untreated soil but increased (35%) in CM (cow manure)-treated soil compared to the bulk zinc particles. Plants in the CM-treated soil showed a higher concentration of zinc in tissues than with those in untreated soil. The shoot Zn percentage for coated and uncoated NPs was 37 and 32%, respectively, which is more than that of bulk Zn (20.6%) (Moghaddasi et al. 2017). Mahajan et al. (2011) found that ZnO NPs at 20 ppm produced the best growth results in mung (*Vigna radiata*) seedlings. For gram seedlings, ZnO NPs at 1 ppm caused an increase of 53.13% in roots and 6.38% in shoots. Above these concentrations, growth retardation was observed in both plants. In rice, nano-form ZnO showed better results by registering an increment of 26 and 25% in fresh weight of shoot biomass and 30 and 23% for root biomass at concentrations of 50 and 100 ppm, respectively, as compared to bulk ZnO, while 500 and 1000 ppm ZnO nanoparticles produced unfavorable effects on growth (Singh et al. 2018). In another study, the application of 2 mg/L ZnO NPs enhanced root elongation of radish and rape seeds and the same concentration had improved ryegrass seedling growth (Lin and Xing 2007). Zhao et al. (2013) reported that the application of 400 and 800 mg/kg ZnO NPs to a soil mixture enhanced cucumber (*Cucumis sativus*) growth.

However, the toxic effects were also registered at high nanoparticles concentrations. Since most plants require merely 0.05 mg/L Zn in soil solution for normal growth, applying higher levels of Zn may lead to phytotoxicity. The rest of the studies are summarized in Tables 2.1 and 2.2.

Table 2.2 Summary of toxicity studies of nanoparticles in plants

S. No.	Nutrient	Nanoparticle type and particle size	Plant	Results	Reference
1	Cu	CuO (231 ± 16 nm and less than 50 nm)	Cucumber (*Cucumis sativus*)	Photosynthesis rate was reduced by 30%, while transpiration rate was reduced by 17% when seedling leaves were exposed to 200 mg/L of nano-CuO, compared with control. Also, fruit firmness was significantly reduced by all Cu treatments, except nCuO at 100 mg/L, compared to the control	Hong et al. (2016)
2	Cu	Cu NPs (40 nm)	Cucumber (*Cucumis sativus*)	The exposure of plant with nano-copper decreased sodium, potassium, phosphorus, sulfur, molybdenum, and zinc concentrations. Eleven amino acids were significantly up-regulated after the treatment of plants with nano-copper. The up-regulation of these amino acids is possibly a defense mechanism of the plants	Zhao et al. (2016)
3	Cu	CuO NPs (30 ± 10 nm)	Cotton (*Gossypium* spp.)	The growth and development of transgenic and conventional cotton w.r.t. root length and number, height, and biomass production were reduced significantly at concentrations greater than 10 mg/L of CuO NP. Moreover, NPs further affected the uptake of nutrients like B, Mo, Mn, Mg, Zn, and Fe, and inhibited the transport of Na and Mn in cotton plants	Le Van et al. (2016)
4	Cu	CuO NPs	Soybean (*Glycine max L.*)	CuO NPs at 500 mg/L reduced the shoot growth, weight, and total chlorophyll content. Hydrogen peroxide level, POD activity, and lignin contents of roots increased on exposure to 100, 200, 400, and 500 mg/L of CuO NPs. CuO NPs cause lignification of root cells and thereby affect root development in soybean seedlings	Nair and Chung (2014)

(continued)

Table 2.2 (continued)

S. No.	Nutrient	Nanoparticle type and particle size	Plant	Results	Reference
5	Cu	CuO NPs (<50 nm)	Rice (*Oryza sativa*)	Exposure to 1000 mg/L of CuO NP decreased the germination rate, number, and size of stomata of the rice plant. At the same concentration, external damage to the root surface was observed. There was a decrease in plant root and shoot growth compared to control at concentrations above 100 mg/L	Da Costa and Sharma (2016)
6	Cu	Cu NPs	Cilantro (*Coriandrum sativum*)	Nano-CuO at a concentration of 20 and 80 mg/kg reduced the relative germination of cilantro by almost 50% as compared to control. The nanoparticles reduced shoot elongation by 12.4% at 80 mg/kg concentration. All the treatments reduced phosphorous accumulation	Zuverza-Mena et al. (2015)
7	Cu	CuO NPs	Green pea (*Pisum sativum* L.)	A concentration of 100, 200, 400, and 500 mg/dm^3 of CuO NPs significantly reduced shoot and root lengths. Exposure to these concentrations also increased the reactive oxygen species (ROS) generation and lipid peroxidation	Nair and Chung (2015a)
8	Cu	CuO NPs	Mung bean (*Vigna radiata* L.)	At 500 mg/L of CuO NPs, the shoot growth, weight, and total chlorophyll content decreased significantly. Exposure to all concentrations of CuO NP significantly reduced the root length and fresh weights of plant. The hydrogen peroxide level, POD activity, and lignin contents of roots increased substantially when exposed to 100, 200, 400, and 500 mg/L of CuO NPs	Nair et al. (2014)
9	Cu	CuO NPs	Mustard (*Brassica juncea*)	Exposure of plant to 100, 200, 400, and 500 mg/dm^3 CuO NPs decreased the root and shoots lengths and increased ROS species and lipid peroxidation significantly	Nair and Chung (2015b)

(continued)

Table 2.2 (continued)

S. No.	Nutrient	Nanoparticle type and particle size	Plant	Results	Reference
10	Cu	CuO NPs (less than 50 nm)	Rice (*Oryza sativa*)	CuO NPs and Cu^{2+} greatly inhibited the elongation and biomass of rice roots after 72-h exposure. Data suggested that growth inhibition, higher ROS production, and gene expression inhibition may be caused by NPs and ions	Wang et al. (2015b)
11	Cu and Zn	CuO NPs (<50 nm) and ZnO NPs (<100 nm)	Bean (*Phaseolus vulgaris*)	CuO NPs at 250 and 500 mg/kg significantly inhibited the growth of root and shoot in plants compared to control. CuO: ZnO NPs increased soluble Cu, Zn, and Ca content by 26, 127, and 4.5 folds, respectively but reduced the levels of Fe and Mn by 0.8 and 0.75 folds, respectively. In shoot, Cu and Na content accumulated by 3.8 fold and 1 fold. But Fe, Mn, Zn, and Ca content reduced by 0.4, 0.2, 0.5, and 0.5 folds, respectively, by the use of CuO NP at 500 mg/kg	Dimkpa et al. (2015)
12	Cu, Fe	CuO, Fe_2O_3 NPs	Lettuce (*Lactuca sativa*) seed, radish (*Raphanus raphanistrum*) seed, and cucumber (*Cucumis sativus*) seed	CuO NPs demonstrated a negative impact on the activities of lettuce, radish, and cucumber seeds, while phytotoxicity of Fe_2O_3 was not significant	Wu et al. (2012)
13	Cu, Zn, and Fe	CuO, ZnO, and FeO_x NPs	Lettuce (*Lactuca sativa*)	Prominent inhibition was observed using CuO NPs as compared to Cu ions, which showed that CuO in NP or bulk is more toxic than Cu^{2+} ions. On the other hand, ZnO NPs played similar role as Zn ions in affecting lettuce germination. Fe NPs at low application rates (5–20 ppm) showed 12–26% root elongation of lettuce seedlings	(Liu et al. 2016)
14	Fe	nZVI (20–56 nm)	Rice (*Oryza sativa*)	No visible toxic effects were exhibited by fresh nanoscale zerovalent iron (nZVI) on the rice seedling growth at low concentrations, while there were obvious toxic effects at high concentrations. At high concentration, inhibition rates for root elongation and shoot length were 29.3 and 46.7%, respectively	Wang et al. (2016b)

(continued)

Table 2.2 (continued)

S. No.	Nutrient	Nanoparticle type and particle size	Plant	Results	Reference
15	Fe	nZVI (20–60 nm)	Rice (*Oryza sativa*)	Nanoscale zerovalent iron (nZVI) did not inhibit germination but caused inhibition of rice seedling growth at concentrations more than 500 mg/kg. The maximum length inhibition rates of roots and shoots were 46.9 and 57.5%, respectively. At 1000 mg/kg, nZVI inhibited the rates for chlorophyll and carotenoids, at 91.6 and 85.2%, respectively	Wang et al. (2016c)
16	Fe	Fe_3O_4 (28 nm),	Tomato (*Solanum lycopersicum L.*)	Fe_3O_4 NPs significantly reduced the above-ground dry matter significantly, thereby showing a negative effect on the plant growth	Antisari et al. (2015)
17	Fe and Cu	Fe NPs (20–30 nm) and Cu NPs (15–30 nm)	Wheat (*Triticum aestivum*)	Cu and Fe NPs caused increase in glycolysis and starch degradation-related proteins. Moreover, SOD activity increased in seeds treated with Cu and Fe NPs	Yasmeen et al. (2017)
18	Fe, Zn	Iron doped ZnO (Fe@ZnO) NPs (~22 nm for ZnO and ~10 nm for Fe@ZnO)	Green peas (*Pisum sativum L.*)	By treating green peas with Fe@ZnO NP at 500 mg/kg, chlorophyll content (27%) and ROS production (~50%) decreased significantly compared to control. Also, doped ZnO NPs were less toxic than bare ZnO NPs in terms of zinc uptake, chlorophyll content, and ROS production	Mukherjee et al. (2014)
19	Fe, Zn, and Cu	nFe_3O_4 (50–100 nm), nZnO (50 nm), and nCuO (40–80 nm)	Maize (*Zea mays*) and rice (*Oryza sativa*)	Out of the tested metal oxide NPs, a significant reduction in the root elongation of maize and rice plants was caused by nCuO (95.73% for maize and 97.28% for rice) and nZnO (50.45% for maize and 66.75% for rice) at concentration of 2000 mg/L. A minor phytotoxicity was also registered by nAl_2O_3 in maize	Yang et al. (2015)
20	Zn	ZnO	Barley (*Hordeum vulgare* L.)	ZnO NPs affected the chlorophyll content and antioxidant levels after 21 days of planting the seedling. Results showed that at 20 mg/kg of ZnO NPs, the concentrations of Zn stressed the plants	Doğaroğlu and Köleli (2017)

(continued)

Table 2.2 (continued)

S. No.	Nutrient	Nanoparticle type and particle size	Plant	Results	Reference
21	Zn	ZnO NPs (<50 nm)	Soybean (*Glycine max* (*L.*))	When compared to the control, treatment of soybean plant with 50 mg/kg of soil; ZnO NPs significantly decreased the final root area and root volume by 13 and 16%, respectively, whereas treatment with 500 mg/kg of NPs caused a decrease of 88 and 87% in root area and root volume, respectively. Also, the stem growth was inhibited by 76%, surface area by 82%, stem volume by 88%, and the average diameter was reduced by 25% by the treatment with 500 mg/kg of NPs	Yoon et al. (2014)
22	Zn	ZnO NPs (90 ± 10 nm)	Maize (*Zea mays*) and sudangrass (*Sorghum sudanese* (*Piper*)	ZnO NPs showed no adverse effects at the 400 mg/kg dose, but had a dose-dependent phytotoxicity above 400 mg/kg concentration	Wang et al. (2016a)
23	Zn	ZnO NPs (<100 nm)	Wheat (*T. aestivum*), radish (*R. sativus*), and vetch (*Vicia sativa*)	Zinc oxide NPs affected the plant growth based on plant species as well as soil functionality. Radish weights were significantly inhibited by 38–40% by the treatment of NPs. In vetch plant, the shoot weight was affected as ZnO NPs exhibited higher toxicity than $ZnCl_2$	García-Gómez et al. (2015)
24	Zn	ZnO NPs (30 ± 12 nm)	Corn (*Zea mays L.*) and cucumber (*Cucumis sativus L.*)	1000 mg/L concentration of ZnO NPs significantly reduced root length of corn and cucumber by 17 and 51%, respectively, while no effect on germination was observed. Zn^{2+} was found to be more toxic to cucumber than ZnO NPs	Zhang et al. (2015)
25	Zn	ZnO NPs (<50 nm)	Pea (*Pisum sativum L.*)	Exposure to a concentration of 250 mg/L decreased the longitudinal growth of roots and continued to decrease by 50–60% with respect to controls at concentrations of 500 and 1000 mg/L. Conclusively, an increase in nZnO concentration resulted in shorter root length than that of the control	Huang et al. (2014)

(continued)

Table 2.2 (continued)

S. No.	Nutrient	Nanoparticle type and particle size	Plant	Results	Reference
26	Zn	Nano-ZnO	Soybean (*Glycine max*)	Nano-ZnO caused leaf damage and genotoxicity at the highest concentration, but only for one plant	Priester et al. (2017)
27	Zn	nZnO (24 ± 3 nm)	Corn (*Zea mays*)	Net photosynthesis reduced by 12%, stomatal conductance by 15%, and relative chlorophyll content by 10% at day 20 by the application of nZnO at 800 mg/kg. The yield of the plant was reduced by $nZnO_2$ by 49%	Zhao et al. (2015)
28	Zn, S	Zn NPs (∼95 and ∼80 nm), S NPs (50 and 100 nm)	Mung (*Vigna radiata*)	Even though the use of zinc and sulfur NPs did not affect the seed germination rates to a great extent, the NPs might pose adverse effect on the integrity of mitochondria	(Patra et al. 2013)
39	Zn^{2+}, Cu^{2+}	nZnO (30–40 nm), nCuO (25–55 nm)	Sweet potato (*Ipomoea batatas*)	Adverse effects on sweet potato were observed only at the higher exposure concentrations and were independent of the chemical form of the metal. It was also reported that the bioavailability followed the trend: Zn > Cu > Ce	Bradfield et al. (2017)

2.2.4 Copper (Cu) NPs

Copper is one of the essential micronutrients which play a role in the synthesis of chlorophyll and protein and carbohydrate metabolism. It has been found that 70% of copper is found in chloroplasts. Copper deficiency may lead to necrosis of apical meristem, retarded growth, bleaching, and crop yield loss. Moreover, copper deficiency in plants affects growth, seed and fruit formation. Other effects include the lignification of cell walls in higher plants (Rai et al. 2018). The use of copper nanoparticles in plants increased shoot: root ratio in lettuce seedlings (Shah and Belozerova 2009). Lee et al. (2008) found that at concentrations more than 200 mg/L, CuNPs caused adverse effects in mung beans and wheat plants grown in Cu NPs modified agar such as reduced root and shoot length (Lee et al. 2008). However, copper nanoparticles are found to cause less oxidative stress than free copper ions (Manceau et al. 2008). In a study of the effect of copper nanoparticles on zucchini (*Cucurbita pepo*), it was found that 1000 gm/L Cu NPs had similar effects as 100 mg/L of $CuNO_3$. In addition, Cu NPs resulted in slower plant growth rate as compared to control (Stampoulis et al. 2009).

Apart from studies focused on the effects of nanoparticles on plant growth and function, copper nanoparticles have also been studied for its effects on soil nitrification process. It was reported that nano-copper had a negative impact on soil nutrient cycles. The negative effects were observed at 1–100 mg/L concentration. Dissolution of Cu^{2+} and production of ROS can be reasons for reduced nitrification kinetic rate. With increasing aging time, $Cu^{(0)}$ NPs oxidized to form copper(II) oxides and copper hydroxides. The study concluded that copper nano-fertilizers need to be evaluated further for their toxicity to microbes in the soil (VandeVoort and Arai 2018). The rest of the studies are summarized in Tables 2.1 and 2.2.

2.2.5 Molybdenum (Mo) NPs

Molybdenum is one of the least abundant micronutrients in plant tissues and is therefore often used as a basis for comparison and measurements of all other nutrients (Kaiser et al. 2005). The nutrient is not biologically active but is a predominant part of organic pterin complex (molybdenum cofactor or Moco). Moco essentially binds to enzymes like molybdoenzymes which require molybdenum in most systems like plants, animals, and prokaryotes (Williams and Da Silva 2002). In the Brassicaceae family especially, molybdenum deficiencies are visually pronounced including mottling, leaf cupping, gray tinting, and flaccid leaves which are found on seedlings that remain dwarfed until dying (Hewitt and Bolle-Jones 1952).

Taran and colleagues studied the effect of colloidal solution of nanoparticles of molybdenum (CSNM) on microbial composition in the rhizosphere of chickpeas. Compared to the control, the treatment of chickpea seeds before sowing increased the development of oligotrophic bacteria in the rhizosphere by 94% at the initial emerging stage and by 3.2 times at flowering stage as compared to control. Also, the use of CSNM along with microbial preparation increased the number of micromycetes by 20% during the initial emerging stage and by 52.9% during the flowering stage, when compared to the control. Therefore, the application of Mo NPs alone or in conjunction with the microbial treatment could enhance the performance, yield, and disease resistance of legume and other crop species (Taran et al. 2014).

2.3 Uptake of Nanomaterials in Plants

To understand the accumulation and uptake of nanoparticles in plants, only a small number of studies have been reported. This section focuses on studies of uptake of nanomaterials by various plants and is not limited to micronutrient nanoparticles. The reported nanomaterials include copper, zinc, iron, quantum dots, and carbon nanomaterials.

The root uptake of ZnO NPs in ryegrass was reported by Lin and Xing (2008), where they found that root zinc content reduced with increasing concentrations (>100 mg/L) of ZnO nanoparticles or Zn^{2+} in the nutrient solution. Root Zn content for ZnO nanoparticles (1000 gm/L) was 3.6 times higher than that of the Zn^{2+} at the same concentration. SEM images of ryegrass roots showed evident ZnO NPs and their aggregation on the root surface and increased with ZnO concentration; however, no such adherence was found in control and Zn^{2+} treated roots. Shoot Zn contents remained low under the ZnO nanoparticle treatments (0.25–1.36 mg/kg) and were much lower than that under the Zn^{2+} treatments (0.25–19.1 mg/kg) (Lin and Xing 2008). The study of uptake pathway of ZnO nanoparticles in maize (*Zea mays*) plants demonstrated that the ZnO NPs were mainly present in the epidermis, some in the cortex and root tips and some even entered the vascular system. However, no zinc nanoparticles were found to translocate to shoots. Further, the experiments showed that the majority of zinc uptake was from zinc ions released from zinc oxide nanoparticles and the zinc accumulated in the plants in the form of zinc phosphate (Lv et al. 2015).

Lin et al. (2009) studied the uptake and translocation of carbon nanomaterial in rice (*Oryza sativa*) plants and proposed plausible mechanisms for nanoparticle uptake. C70 nanoparticles may enter roots through osmotic pressure, capillary forces, or via highly regulated symplastic route. Once in the plant roots and stems, C70 nanoparticles may share the vascular system with water and nutrients and may be transported via transpiration (Lin et al. 2009).

Likewise, various studies have reported the accumulation of metals due to metal nanoparticles in cellular compartments like vacuoles, cell wall, and nuclei (Schwab et al. 2016), and that these nanoparticles affect many physiological and biochemical process (Lin and Xing 2007, 2008; Zhao et al. 2012a, 2013; Mukherjee et al. 2014; Wang et al. 2018). A study by Zhu and colleagues on pumpkin plants grown in an aqueous medium containing magnetite (Fe_3O_4) nanoparticles showed that plants can absorb, translocate, and accumulate the particles in the tissues. Even though the study was conducted in plant growth medium with high concentrations of magnetite nanoparticles, it clearly showed the accumulation of particles in roots and in the leaves. To study the real impact, the plants were grown in sand with magnetite nanoparticles and it was observed that the level of uptake and accumulation were reduced significantly as compared to those grown in liquid media. Measurable levels of magnetic signals were detected in all tissues, ranging from <0.1 memu/g to 0.4–1.2 memu/g in leaves, and stems close to root. No magnetic signals were detected in the plants grown in soil. These results suggest that interactions between plants and particles need a deeper understanding. All the aspects of the ecological system need to be taken into consideration (Zhu et al. 2008).

Adhikari and co-workers in their solution culture experiments on the growth and enzymatic activity of maize gave the possible explanation for the entry of nanoparticles into the plant system. Since the plant cell wall acts as a barrier with pore diameter of 5–50 nm, only nanoparticles with diameter less than that of the pore diameter of cell wall can easily pass through it. Another plausible explanation includes the small size and high kinetic energy of these nanomaterials. When the nanoparticles enter the cell wall, it may cause the enlargement of cell wall pore size. This can lead to new induced and larger pore size of cell wall which may lead to entry of larger sized nanoparticles into the plant system. Nanoparticles may enter the plant roots through osmotic pressure and capillary force and consequently translocate through the intercellular plasmodesmata (Adhikari et al. 2016). Permeation of nanoparticles applied to leaf surface is also possible through the stomatal openings or through the bases of trichomes. Cuticular nanopores can be another point of entry for nanoparticles. However, the mechanism of foliar absorption of nanoparticles is not well understood (Adhikari et al. 2016).

2.4 Toxicity Aspects of Nanoparticles

Nanomaterial-based micronutrients must be assessed and analyzed fully for their toxicological aspects before putting them into regular use. This section discusses some of the toxic effects of nanoparticles on plants. The compiled studies pertaining to the toxicity aspects of various micronutrient nanoparticles on plants have been listed in Table 2.2. Lin and Xing (2007) studied the influence of five different types of nanoparticles such as multi-walled carbon nanotubes, aluminum, alumina, zinc, and zinc oxide on seed germination and root growth of size plants namely radish, rape, ryegrass, lettuce, corn, and cucumber. The results obtained showed that seed germination was only affected in the case of ryegrass and corn. It was seen that root growth reduction varied from species to species and the type of nanoparticles used. In ryegrass, ZnO NPs reduced biomass and caused shrinkage of the roots (Lin and Xing 2007). Shaw and Hossain (2013) studied the effect of copper oxide nanoparticles (<50 nm in size) on rice plants. It was seen that seed germination was significantly reduced, root cells were damaged, H_2O_2 levels increased, proline accumulated, and levels of carotenoids decreased. It has been found that the effect of NPs accumulation depends on their size, concentration, and surface chemistry, as well as the chemical milieu of the subcellular sites where the nanoparticles are deposited (Dietz and Herth 2011). In recent study, it has been reported that maize seedlings which were exposed to different concentrations of tin (Sn) NPs for 15 days have shown the enhanced expression of oxidative stress-related marker enzymes like guaiacol peroxidase, polyphenol oxidase, and catalase activity (Pudake et al. 2019).

Effects of ZnO nanoparticles on plants are probably the most widely studied. It has been reported that ZnO NPs affect the growth of ryegrass plant (Lin and Xing 2007, 2008), maize (Lin and Xing 2007), rice (Boonyanitipong et al. 2011), zucchini (Stampoulis et al. 2009), wheat (Dimkpa et al. 2012), soybean (Yoon et al. 2014), cucumber (Zhao et al. 2013), and buckwheat (Lee et al. 2013b), and the toxic effects were dose-dependent (Wang et al. 2018).

The exact mechanisms of possible phytotoxicity of nanoparticles remain unknown, and only theories have been given. The generation of reactive oxygen species by metal oxide nanoparticles can be one of the reasons (Choi and Hu 2008). ROS can induce DNA damage (Mehrabi and Wilson 2007), can be signaling molecules of abiotic and biotic stresses (Takahashi et al. 2011), and can also control programmed cell death (Gechev and Hille 2005). Moreover, NPs may cause genotoxicity when they enter cells (Karlsson 2010). Plants possess antioxidant system which includes both enzymatic and non-enzymatic antioxidants like catalase, superoxide dismutase, and ascorbate peroxidase. However, when the balance between reactive oxygen species and antioxidant defense is disturbed, oxidative stress occurs (Gajewska and Skłodowska 2007).

The extent long-term effects of engineered nanoparticles in plants are still unknown (Rico et al. 2011). Albeit, the oxidative damage caused by copper ions (Cu^{2+}) is well known (Balestrazzi et al. 2009; Macovei et al. 2010). Many toxicity studies on copper nanoparticles on plants, or soil nitrification and soil flora fauna have not focused on soil–plant system at all. Copper nanoparticles may cause potential damage to plant DNA via redox interactions (Atha et al. 2012; Lee et al. 2013a). The potential mechanism of copper nanoparticle toxicity toward soil microbiome and plants may be caused by the release of copper ions from nano-form, increased ROS levels, and the decrease in particle size to nanoscale. These assumptions, however, require more analysis (Anjum et al. 2015).

2.5 Conclusion and Future Aspects

The rise in population means a rise in agriculture demands, and to meet the growing needs, we need advanced technology and methods to sustainable growth and development. The new trends in nanotechnology have shown a new ray of hope in combatting food security issues. Nanotechnology may play a pivotal role in fighting against micronutrient deficiency in the future. Nanotechnology is still a newer perspective in research and requires in-depth knowledge and understanding. It is highly desirable that before implementing nanomaterial-based products in agricultural use, their mode of action, mechanism, toxicity aspect, and long-term side effects in the ecological system be deeply studied. There is also a need for a regulatory framework to ensure the safe use of these rather new materials. Having unique physicochemical properties, nanomaterials are currently being explored as an alternative to current micronutrients.

The commercialization of nanotechnology-based products has already been started. Several foods and personal care items are using engineered nanoparticles (Kessler 2011; Lorenz et al. 2011; Smijs and Pavel 2011; Weir et al. 2012). The use of nanoparticle-based micronutrient products is only a matter of time and further studies. Several studies pertaining to the effects of micronutrient nanoparticles have been undertaken by various groups albeit, the exact mechanism and mode of function is still a lesser-known part of the works. Nanoparticles have been used to enhance the growth of plants. It is also of great interest to reduce the dependency of the plant on the type of soil for micronutrient requirements. This might enable the growth of crops on average or poor-quality soil and put low-quality lands into use. Studies depicting enhanced plant growths also show that a lesser amount of nanoparticles can bring about a considerable change in plant growth.

However, every coin has two sides. Many studies have reported the retarded growth or other toxic effects like oxidative stress on plants. Increasing the concentration of nanoparticles above the optimum levels caused undesirable effects. Moreover, the persistence of these nanoparticles in the environment and transfer from plants and soil to humans along the food chain is another perspective that requires more research. So, it is safe to say that we are still progressing at the development stage of nanoparticles as micronutrients. However, to support the sustainable development of nanotechnology, potential risks, whether real or imagined, have to be evaluated based on sound, risk-focused research that addresses all relevant aspects of the concern.

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Chapter 3
Nano-biofertilizers: Harnessing Dual Benefits of Nano-nutrient and Bio-fertilizers for Enhanced Nutrient Use Efficiency and Sustainable Productivity

Anu Kalia and Harsimran Kaur

Abstract Nanotechnology has introgressed to several disciplines of science and technology besides recent applications for improving the crop production and environmental sanctity of the arable lands. Though incipient, an impetus has been observed for the development of new-age smart nano-fertilizers which include both novel formulations of conventional fertilizers and adsorbed/encapsulated nano-nutrients. The phyto- and eco-toxicity issues of these novel nano-scale fertilizers have further escalated the need for alternatives that can diffuse the negative application effects of nano-fertilizer alone. The most feasible improvement can be nano-biofertilizers—a conjugate preparation involving combinatorial application of nano- and bio-fertilizers (including an array of soil beneficial microbes) to obtain enhanced and sustainable crop productivity with better addressal of environmental safety.

Keywords Bio-fertilizer · Nano-delivery · Nano-fertilizer · Nutrient pay-load · Sustainability · Use efficiency

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3.1 Introduction

Soil plays a central role in crop productivity and serves to fulfil human requirements of food and nutrition. Soil being a finite natural resource requires care and maintenance for indefinite use by the coming generations (Singh 2018). Soil functions as a dynamic matrix and is a living component for facilitating plant growth besides serving as a habitat for various macro- and microorganisms (Timilsena et al. 2015; Singh 2018). It holds different essential nutrients (seventeen in total with six major, eight micro- and three structural nutrients) in specific quantity required by the plants to achieve proper growth and development. Further, it supplies nutrients in available forms to the growing plant. However, growing population pressure has forced agriculture to be driven by economy and thus, primarily aimed for increased crop productivity and food supply to sufficient levels (Daniyan et al. 2017). Incessant exploitation of the arable land and soil natural resources has led to deterioration of soils leaving behind famished nutrient-poor soils incapable of sustaining high crop productivity (Daniyan et al. 2017; Li et al. 2017). Therefore, in order to retain higher crop yields, soil quality and its fertility has to be sustained through improvement of soil physical and chemical characteristics (Miao et al. 2015; Tian et al. 2015; Li et al. 2017). Modern agriculture is currently working with diverse objectives, including higher productivity with sustained use of fertilization, lower production costs and evaluating crop-related effects on the environment, to name a few (Yousaf et al. 2017).

3.1.1 Fertilizers and Their Role for Crop Productivity

Soil needs to be replenished with the right amount of nutrients so as to sustain soil fertility and thereby maintain improved produce quality and quantity. Certain extraneous substances as soil amendments, manures, organic or inorganic synthetic fertilizers are added to the soil for such nutrient replenishments. The Green Revolution era involved the use of commercial synthetic fertilizers for obtaining on an average about 30–50% higher crop yield (Timilsena et al. 2015). Fertilizers are chemical substances/nutrients combined together, used primarily as a plant nutrient content for ensuring higher crop yield and productivity. These are composed of a wide range of natural and fabricated materials and are available in liquid, solid as well as gaseous forms (Timilsena et al. 2015). Fertilizers are usually categorized into natural or synthetic, organic or inorganic, simple or complex as per their origin and nature of material used, and generally claim to boost soil nutrient levels available to plants and a consequent plant growth promotion (Timilsena et al. 2015). Addition of all-ingredient fertilizers work on various levels to perk up the physical (soil porosity, friability, absorption), chemical (acidity and nutrient availability) as well as biological (living biomass as microorganisms) properties of soil. Therefore, the requirement and the ultimate application of fertilizers reload the soil with essential nutrients drained by crop harvest and improve crop productivity (Sharma and Chetani 2017).

3.1.1.1 Fertilizer Application Techniques

Several studies based on conventional fertilizers reflect that only a small fraction of the applied fertilizer is actually taken up by plants. Therefore, the nutrient supply is usually incompatible with the plant requirements (Timilsena et al. 2015). Fertilization methods mainly depend on the type of cropping system, fertilizer material and equipment used by the cultivator. Broadcasting, banding, side dressing, fertigation and foliar feeding are the common fertilizer application techniques in practice (Savoy 2012). However, these traditional fertilizer application methods trigger ineffective fertilization causing loss of a major proportion of the fertilizer (Rahman and Zhang 2018).

3.1.1.2 Tackling the 'Over-Fertilization' Peril

Over-fertilization, extreme and indiscriminate use of fertilizers, often results in high levels of land, atmospheric and water pollution. Further, it also results in a simultaneous decline in crop productivity and product quality. This practice is popular among the growers in aspiration to obtain higher yields. Unfortunately, it has led to cropping up of numerous economic and environmental complications besides a major decline in effective utilization of nutrients by the crop, the nutrient use efficiency (Yousaf et al. 2017; Rahman and Zhang 2018). Some of the prime environmental tribulations transpiring from over-fertilization include soil acidification, high N_2O emissions leading to global warming through the greenhouse effect, heavy metal accumulation, eutrophication, blue baby syndrome, presence of harmful algae in water, exhaustion of soil organic ratio and other adverse complications (Timilsena et al. 2015; Rahman and Zhang 2018). Over-fertilization has also led to imbalance in nutritional profile of the soil causing appearance of multiple nutritional deficiencies due to preferential mining of specific nutrients and non-replenishment of soil nutrients because of improper fertilization. This eventually has resulted in lowering of the crop yields, in quality as well as in quantity (Timilsena et al. 2015). Therefore, the in-practice conventional fertilizers are insufficient to sustain agricultural ecosystems and need enhancement in their properties to be more competent (Timilsena et al. 2015). Likewise, an efficient and sustained use of fertilizers is essential for enhanced nutrient efficiency and reduced losses. A study in rice and oilseed rape showed increased yield with balanced mineral fertilizer input (Yousaf et al. 2017). However, the positive or negative impacts of inorganic fertilization on edaphic characteristics cannot always be traced downed to attain specific conclusions as the soil organic carbon (SOC) vary considerably according to soil type, fertilization history, climate and existing soil nutrients and carbon, thus making it quite difficult to optimize the fertilizer application pattern (Li et al. 2017). Therefore, the challenge is to establish a balance between fertilizer utilization and soil quality so that food demands are fulfilled incessantly while keeping the soil healthy with nominal or negligible environmental damage (Singh 2018).

3.1.2 Organic Fertilization: Aiming for Eco-Friendly Green Revolution

The adversity of chemical fertilizers has led to a shift in agricultural approaches from agrochemicals to green technology, such as bio-conversion, bio-refinery and bio-based organic fertilizers, in order to attain bio-safety in food and energy supplies. Organic production system is being endorsed to enhance nutrient supply and field management, thus improving the soil biodiversity and food safety (Bhardwaj et al. 2014; Madhavi et al. 2016). It intends to sustain ecosystem and soil health besides boosting economy through improved food production (Islam et al. 2017). This technology is on the go worldwide for its applicability in waste disposal by conversion of biodegradable waste into organic fertilizers/compost, while preventing soil erosion and carbon losses (Daniyan et al. 2017).

In contrast to the inorganic fertilizers with peaked prices and environmental issues, organic fertilizers come cheap and are eco-friendly. These fertilizers aid in improving physical, chemical and biological components of soil, besides triggering better root growth in plant for enhanced nutrient/fertilizer uptake efficiency (Ukoje and Yusuf 2013; Raimi et al. 2017). Studies have indicated production of increased contents of plant metabolites of antioxidant importance with application of organic fertilizers compared to the traditional inorganic fertilizers (Raimi et al. 2017). On the contrary, there are certain challenges associated with the use of organic fertilizers. These may include usually slow rates of decomposition, variation in nutrient ratio and inadequate nutrient supply, its pungent smell and serves as a potential source of pathogenic microbes and at times, heavy metal contaminants (Ukoje and Yusuf 2013; Raimi et al. 2017). Such challenges have prompted the need to figure out more efficient nutrient management practices so as to attain an economical way in nutrient management, thereby emphasizing the role of sustainable agriculture to ensure resource effectiveness (Raimi et al. 2017). Therefore, these shortcomings of inorganic and organic fertilization techniques individually have led to adoption of an approach for integrated use of the both fertilizers over the years (Kong et al. 2014; Li et al. 2017).

3.2 Bio-fertilizers: Pursuit for Sustainable Agricultural Productivity

One approach that has gained popularity in terms of being bio-safe, efficient in nutrient management and providing higher productivity with nutrient-loaded produce, is the use of beneficial and efficiently working microorganisms including bacteria, blue–green algae to fungi, as biological fertilizers or bio-fertilizers (Lutful et al. 2012; Latha et al. 2013; Olanrewaju et al. 2017; Raimi et al. 2017). These are an integral part of organic farming and nutrient management practices as bio-fertilizers promote higher produce levels and better soil health through an eco-friendly, cost-effective and renewable approach. Further, biofertilizers exploit a natural and biological system of nutrient utilization to replace or supplement the conventional fertilizers in agricultural systems (Mishra et al. 2013; Jehangir et al. 2017). This nutrient fertilization approach has the potential to supplement or slowly substitute the use of environmentally unhealthy chemical fertilizers while promoting sustainable agriculture (Olanrewaju et al. 2017; Raimi et al. 2017).

Bio-fertilizers include microbes which help in mobilization of essential plant minerals thereby helping in avaialbility of these elements for uptake and better growth (Yasin et al. 2012). These could be 'live or latent cells of microorganisms, which when applied to plant surface, seed, root or soil, colonize the rhizosphere or the plant interior and enhance soil fertility while rendering plant nutrients and growth substances available to crops for better plant growth and health' (Vessey 2003; Raimi et al. 2017). Mechanistically, bio-fertilizers offer diverse actions spanning over plant growth promotion through availability of nutrient by nitrogen fixation, phosphate-, zinc-, potash solubilization, production of growth hormone (IAA, GA, etc.) and enhancement in number and functional properties of plant growth-promoting microbial populations (Boraste et al. 2009; Rashid et al. 2016; Raimi et al. 2017; Ju 2018) (Table 3.1).

These competent microorganisms may be either rhizospheric (colonize intercellular spaces or external surface of plant roots) or endophytic (colonize the apoplastic spaces or the tissues in plants) in terms of their spatial occurrence (Gupta et al. 2012; Olanrewaju et al. 2017; Raimi et al. 2017). Further, these microbes can secrete and make available diverse primary and secondary metabolites such as vitamins and minerals, antibiotics and proteins that improves the crop's resilience to tolerate abiotic (drought, salinity, presence of heavy metals) and biotic stresses (soil and root borne pathogens) besides helping in soil fortification (Jehangir et al. 2017) (Fig. 3.1). Also, some plant–endophyte interactions are being employed to degrade and/or eradicate the evapotranspiration of the volatile organic pollutants such as trichloroethylene, benzene and xylene released by plants (Moore et al. 2006; Wu et al. 2009). Therefore, incorporating bio-fertilizers in agriculture can play a remarkable role in increasing soil fertility, soil biodiversity and yield attributing parameters leading to an enhanced overall yield (Mishra et al. 2013; Ritika and Utpal 2014).

However, commercial availability of high-quality efficient bio-fertilizers has been the major bottleneck for their widespread reach and impact. Certain shortcomings responsible for this include the carelessness of the biofertilizer production and marketing houses in ensuring the product quality and desynchronized interactions among the scientists and extension workers (Pathak and Kumar 2016). Therefore, sustainability of crop productivity and environmental health can be preserved through widespread and efficient implementation of bio-fertilizer-based integral nutrient management systems or in conjugation with some novel fertilizer formulations (Bhardwaj et al. 2014; Ju 2018).

Table 3.1 Mechanism of action of bio-fertilizers for improving the plant growth and development

Mechanism	Impact	Microbes involved	References
Direct mechanism			
Nitrogen fixation	Converts atmospheric nitrogen to plant usable forms (ammonia, nitrates, nitrites) through nitrogenase activity	*Rhizobium, Azotobacter, Azospirillum, Frankia*	Pathak and Kumar (2016)
Phosphate solubilization	Converts organic forms of phosphate to inorganic soluble forms through organic and inorganic acids, phosphatase, phytase action	*Pseudomonas, Bacillus*	Raimi et al. (2017)
Siderophore production	Responsible for iron uptake	*Chryseobacterium*	Olanrewaju et al. (2017)
Phytohormone production	Acts through production of growth-promoting hormones such as auxins, gibberellins, cytokinins	*Pseudomonas, Achromobacter, Sinorhizobium*	Vejan et al. (2016)
ACC deaminase activity	Reduces the effect of stress ethylene	*Microbacterium, Bacillus*	Bal et al. (2013), Glick (2014)
Indirect mechanism			
Antibiotic production	Bio-control action through production of secondary metabolites such as phenazines, phloroglucinol, pyrrolnitrin and subtilin to control and eliminate plant pathogens	*Bacillus, Pseudomonas*	Premachandra et al. (2016)
Vitamin production	Improves crop yields through enhanced microbial processes	*Azotobacter*	García-Fraile et al. (2015)
Induced systemic resistance	Act through activation of various resistance mechanisms in plants	*Pseudomonas*	García-Fraile et al. (2015)
Lytic enzyme	Bio-control action through production of various enzymes such as chitinase and glucanase.	*Bacillus*	Olanrewaju et al. (2017)
Quorum quenching	Degradation action on various quorum sensing signals from phytopathogens	*Rhodococcus, Bacillus*	Alagarasan and Aswathy (2017), Zapata et al. (2017)
HCN production	Act synergistically with other bio-control mechanisms	*Rhizobium, Pseudomonas*	Olanrewaju et al. (2017)

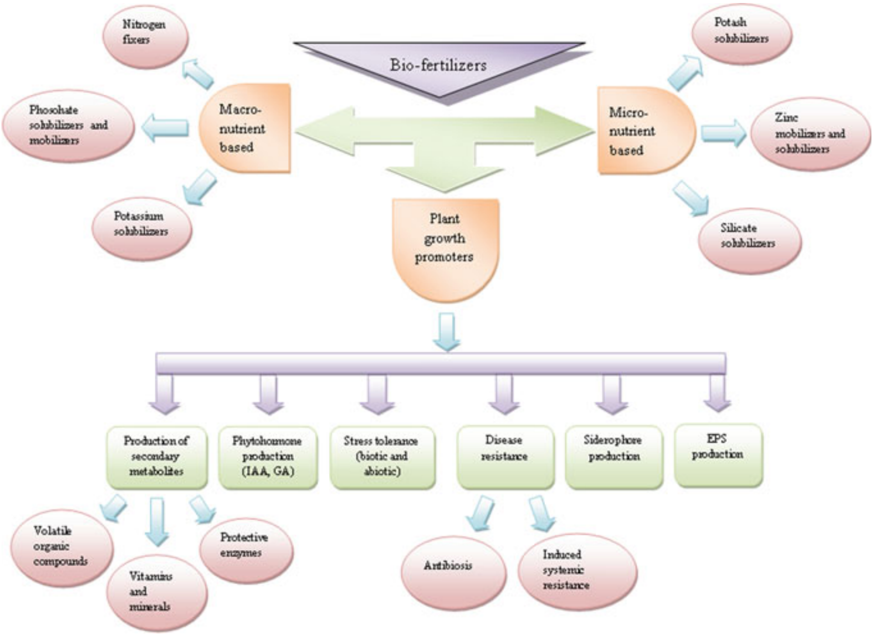

Fig. 3.1 Bio-fertilizers-their types and mechanism of action for plant growth promotion

3.3 Nano-fertilizers

Nanotechnology has been emerging as an innovative scientific field introducing the new age of nano-agriculture to revolutionize crop cultivation and nutrition application approaches through use of various novel devices and products for enhancing crop productivity (Subramanian and Tarafdar 2011; Mardalipour et al. 2014). The matter at nano-scale exhibits variable properties in comparison to their bulk counterparts due to reduced molecular size and altered molecular interactions (Axelos and Van de Voorde 2017). The ultra-small size allows the nanoparticles to have large surface area-to-volume ratios. Further, the presence of more number of surface atoms enhances the reactivity for various chemical, physical and biological reactions (Mardalipour et al. 2014; Rai et al. 2015; Madhavi et al. 2016). Some of these properties have great potential in agriculture such as increased bioactivity and bioavailability due to greater surface area, more reactivity, surface and adherence effects (Guo et al. 2014; Singh et al. 2017).

3.3.1 Conventional Fertilizers Versus Nano-fertilizers

The Green Revolution era advocated extensive use of chemical fertilizers for obtaining higher productivity which rather led to several complications such as depreciation of the soil fertility, appearance of micronutrient mineral deficiencies in agradable soils leading to decrease in crop productivity. Conventional fertilizers exhibit low use efficiency, and less nutrient uptake potentials. A consequent deteriorating effect of these fertilizers on soil and environmental health is primarily due to rapid conversion of nutrients to plant unavailable forms. The applied nutrients exhibit losses through several processes such as run-off, leaching, photo-volatilization and other losses resulting in emission of greenhouse gases and eutrophication (Raliya et al. 2018). These problems of conventional fertilizers have brought nanotechnology to the frontline for the development of smart fertilizers to end the practice of indiscriminate use of fertilizers and promotion of sustainable agriculture (Raliya et al. 2018) (Fig. 3.2).

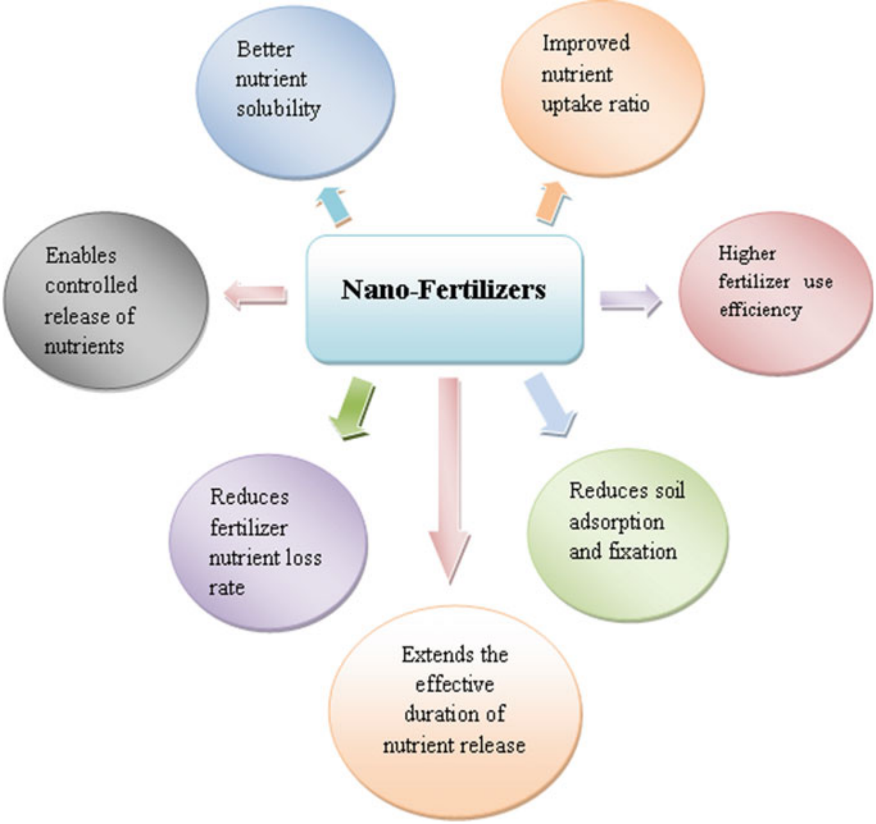

Fig. 3.2 Nano-versus-conventional fertilizers: improved traits of nano-fertilizers over conventional fertilizers

3.3.2 What Are Nano-fertilizers?

Application of nanotechnology in agriculture mainly revolves around providing plant nutrients through development of efficient delivery vehicles containing macro- and micronutrient fertilizers (Rai et al. 2015; Kah et al. 2018). Nano-fertilizers involve material elements having size with at least one physical dimension in 1–100 nm range which can be derived from otherwise bulk materials (e.g. fertilizer coated with nanoparticles, nano-enabled fertilizers) (Raliya et al. 2018). Precisely, nano-fertilizers can be defined as nutrient fertilizers made, in part or whole, of nano-structured formulation(s) that allows targeted delivery to plants, allowing controlled release and efficient uptake of nutrients, or in simple words, it is a fertilizer in the nanometre regime (Rai et al. 2015; Raliya et al. 2018; Singh et al. 2017). By using nanoparticles as filler or reservoir of fertilizer, nanotechnology may help in fine tuning the existing trends of nutrient management and crop productivity (Farnia and Ghorbani 2014; Mardalipour et al. 2014; Madhavi et al. 2016).

As discussed earlier, nano-fertilizers have been developed to address the problems of conventional fertilizer applications. These aim to improve nutrient use efficiency (NUE) either by enhanced nutrient bioavailability through reduction of nutrient losses to the environment incurred due to fixation, leaching or by targeted and timely release of nutrients (Kah et al. 2018). Some unique features of nano-fertilizers such as high surface area-to-volume ratio, high mobility and solubility, target specificity and low toxicity at optimum concentrations are responsible for improved crop performance. Nano-fertilizers can initiate significant changes in the site and functioning of photosynthesis *viz*., expansion of the leaf area, increase in the rate of photosynthesis, and improvement in the light absorption potentials (harvesting of PAR) such that productivity can be improved with crop plants exhibiting higher dry matter and improved yield. Considering the nutritional and functional relevance, nano-fertilizers can be categorized as macronutrient nano-fertilizers (hydroxyapatite, nano-urea, nano-calcium, nano-sulphur), micronutrient nano-fertilizers (nano-ZnO, nano-CuO, nano-Boron, nano-Mn particles and many more) and nutrient-loaded nano-fertilizers (using nanomaterials as macronutrient carrier such as nano-chitosan-NPK fertilizers) (Kah et al. 2018). This is discussed in detail in next chapter of this book.

3.3.3 Nano-fertilizers in Precision Agriculture

Precision agriculture involves designing controlled systems that improve the use efficiency of the applied agri-inputs both temporally and spatially. The nutrient bioavailability throughout the crop growth period and timely delivery of these nutrients with respect to different stages of crop growth are the features of nano-fertilizers which are specific for very efficient nutrient management in precision agriculture (Singh et al. 2017). The gradual and controlled release of nutrients precisely in response to plant's biological demands will ensure improved uptake of the supplied nutrient. This can be accomplished through the use of specialized polymers or devices which are triggered in response to signals secreted by the plant roots in the environment (Rai et al. 2015; Singh et al. 2017). The nutrient materials/fertilizer may be delivered by various means such as nutrient encapsulation by nanomaterials, encrusted within a thin protective nano-particulate polymeric film, in the form of nano-emulsions or directly as nutrient nanoparticles (Derosa et al. 2010; Rai et al. 2015; Madhavi et al. 2016). Also, gradual release of nutrients can help reduce land and water pollution, prevent eutrophication of water bodies and protect plant from various abiotic and biotic stresses (Rai et al. 2015; Madhavi et al. 2016; Singh et al. 2017).

3.3.3.1 Nano-‘smart’-fertilizers for Slow/Controlled Release of Nutrients

Nano-fertilizers are fabricated as slow/controlled release nutrient fertilizers to ensure sustained and targeted delivery of nutrient at the cellular level. This may be attributed to their unique potential of easy passage through membrane barriers of the plant cell walls, thereby offering an altered absorption dynamics of the applied nano-form fertilizers. Thus, nano-scale formulations of fertilizer nutrients are anticipated to save the non-renewable fertilizer resources such as rock phosphates by improving the nutrient uptake potentials of the test crop(s) and enhanced use efficiency (UE) of the applied nutrients in the soil. As decreasing the fertilizer granule size to nano-scale is expected to enhance the solubility and dispersion potentials, for example, of nano-phosphorus fertilizers derived from sparingly soluble rock phosphates in soil solution, improved P-availability can be ensured. However, this feature will be deleterious if utilized for nitrogenous urea fertilizer where it may lead to faster dissolutions and losses thereof. Therefore, the fast dissolving conventional fertilizers have to be formulated in a manner that their release from the formulation is either slow or precisely controlled/targeted according to the utilization potential and growth stage of the plant (Sempeho et al. 2014; Madhavi et al. 2016; Preetha and Balakrishnan 2017; Jiao et al. 2018).

A surface-modified zeolite phosphate nano-fertilizer formulation was developed by Bansiwal et al. (2006) in India, while in countries such as China, USA, and Germany, various formulations have been developed and are under laboratory analysis (Subramanian and Tarafdar 2011). These formulations must be developed in a way to preserve the key properties of nanomaterials such as stability, effective time-controlled release and targeted delivery of optimum nutrient concentrations, high solubility and bio-safety (Madhavi et al. 2016). Once applied, the uptake, translocation and fate of the nano-fertilizers in plants depend more or less on the age, species and growth environment of the plant involved as well as on the nanoparticles used (Rico et al. 2011; Rane et al. 2015).

Nano-materials can help in promotion of plant growth and yield when used at controlled bio-safety levels (Ditta and Arshad 2015). For example, multi-walled carbon nanoparticles (MWCNP) have been indicated as potential growth promoters in various studies conducted on tomato, tobacco and mustard plant due to substantial increase in seed germination and plant growth upon their application (Rico et al. 2011; Rai et al. 2015; Yuan et al. 2017). Nano-TiO_2 has been reported to enhance the photosynthetic ability and nitrogen metabolism in spinach plants (Rane et al. 2015). Still in its infancy, nano-formulation technology in agriculture has to address numerous ethical and bio-safety issues that necessitate the need for careful evaluation of the nanoparticle impact before these can be established as safe for use (Rai et al. 2015). For complete analysis of the impact of nano-fertilizers, it is important to account for all types of morphological, biochemical, physiological and nutritional changes induced by nano-formulations in plant system, its effect on rhizospheric microflora and nutrient biogeochemical cycles while keeping a check on the fate of nano-products in soil and plant ecosystem under native field conditions (Subramanian and Tarafdar 2011).

3.4 Nano-biofertilizers: Augmenting the Benefits of Nano- and Bio-fertilizers

Conjugated use of mineral nano-nutrients and bio-fertilizers has been suggested as a feasible approach to lower the indiscriminate application of agrochemicals and to enable the integrated nutrient management for sustained crop productivity (Mir et al. 2015; Vejan et al. 2016; Boddupalli et al. 2017; Bashan et al. 2014; Schoebitz et al. 2013). Plant microbiome, microorganisms inhabiting the surface and internal tissues of a crop plant imparting plant health and yield benefits, has an evident role in sustainable agricultural productivity and it has to be reckoned on the forefront before the dawn of nano-smart-fertilizer revolution in agriculture. Nanomaterials cannot be utilized in higher concentrations and quantities as they pose negative effects on crop plants, livestock and the humans. Their use as a fertilizer nutrient or its nano-scale carrier will be jeopardized if their application hampers the growth and development of test plants. Therefore, a mid-way approach that can escalate the benefits of nanomaterial application at lower eco-safe concentrations will be appropriate.

Nano-biofertilizer is a conjugate nanomaterial and bio-inoculant application technology which could ensure timed and targeted delivery of the nutrient to the test crop besides enhancing the functional benefits imparted by the bio-fertilizer component of the formulation (Gouda et al. 2018). However, the efficient development and implementation of these formulations is hindered due to the unavailability of sufficient literature regarding the basic understanding of the various interactions and exchanges between the nanoparticles, plant rhizospheric microflora and plant systems (Boddupalli et al. 2017; Razzaghifard et al. 2017). Since, most of the fertilizers are applied as basal soil doses, application of nanofertilizers through this mode may exhibit variability in the extent of the positive impact imparted on the crop as the soil organic substances including humic and fulvic acids can affect the relative stability and mobility of soil-applied nanomaterials through alteration of their surface charge, zeta potential and thus their hydrodynamic size. These substances may either lead to aggregation of the nanomaterial or enhance their transportation as "organic substance-coated nanomaterial" in soil solution through complexation and stabilization by organic acids in soil (Zhou et al. 2017). The consequence of enhanced stabilization and transportation of the nanomaterial in soil solution is thereby anticipated to affect the soil physical and chemical properties (Jiang et al. 2017) and hence, may also alter the soil biotic components, primarily the soil microflora (Rajput et al. 2017). Moreover, the direct nanomaterial–microbe cell interactions are also quite complex and may elicit some unique variabilities in microbial cell physiology and gene expression which may lead to either proliferation (Pallavi et al. 2016) or diminished diversity and count of certain specific groups of microorganisms inhabiting soil (Simonin et al. 2016). Therefore, it will be prudent to sequester or contain nanomaterials in nano-vehicles to decrease their mobility and hence toxicity to vulnerable soil beneficial microbes. Likewise, such negative effects on soil microbiota can be further decreased by incorporation of nano-primed beneficial plant growth-promoting rhizobacteria (PGPRs) in test plants rather than direct application of nanomaterials (Timmusk et al. 2018).

Several studies under controlled environment and few under field conditions have established the role of different types of nanoparticles as potent agents for improving crop health and productivity through various mechanisms such as suppression of plant diseases, antimicrobial activity, growth-promoting action and many more reviewed in other chapters of this book. For example, a study by Mahajan et al. (2011) indicated enhanced root and shoot biomass and length on application of nano-ZnO, while nano-TiO_2-induced seed germination in fennel was reported earlier (Feizi et al. 2013). However, impact of nanoparticles and their action mechanism towards plant growth-promoting microbes is not sufficiently explored, at least not at an industrial scale or under field conditions (Rico et al. 2011). As per the recent studies, penetration of nanoparticles through cell wall pores and their subsequent accumulation in microorganisms may either enhance or inhibit microbial growth and plant beneficial interactions in a dose-dependent manner (Rangaraj et al. 2014). Moreover, no generalization has been achieved regarding the effect of nanoparticles on microbes as these interactions are highly specific for the type of organism and nanomaterial involved. This necessitates the regulation of nanoparticle discharge into the environment at bio-safe levels so as to protect agronomically important microbes against probable nanoparticle toxicity while allowing the nanoparticle-induced production of environmentally important microbial secondary metabolites (Dimkpa et al. 2012b; Haris and Ahmad 2017). Deciphering the probable interactions taking place between the nanoparticles, plant beneficial microbes and plant systems to develop efficient nano-biofertilizers may mark a step closer to Green Revolution (Vejan et al. 2016).

3.4.1 Contributions of the Nano- and Bio-components of the Nano-biofertilizer

Various studies investigating the effect of nanoparticles on the plant–microbe system have suggested two possible mechanisms for their plant growth-promoting action, i.e. direct mode by enhancing nutrient bioavailability and indirect mode by causing a stimulating effect on PGPRs prior to seed inoculation. These mechanisms provide two different ways of application of the nano-biofertilizers, *viz*., nano-fertilizers and bio-fertilizers being implemented as separate entities or use of nano-interacted/enhanced bio-fertilizers (Gouda et al. 2018). When used as a separate unit with bio-fertilizers, nanoparticles produce certain direct effects on plants such as increased plant enzyme activity, promotion of seed germination, boosting of the plant resistance to adverse conditions, improvement in carbon sequestration and nitrogen fixation, and augmented photosynthetic as well as respiratory processes. Therefore, this largely improves the plant biomass and its nutritional condition, thereby ensuring greater returns from the crops (Taran et al. 2014). Increased germination with better root growth rate on application of multi-walled carbon nano-tubes (MWCNTs) has been recorded in various crops such as tomato, soya bean and corn (Khodakovskaya et al. 2013; Lahiani et al. 2013). Another study by Shende et al. (2017) indicated the growth-promoting effect of colloidal solution of CuNPs on pigeon pea as CuNPs induced greater root and shoot length and biomass as compared to the control plants.

On the other hand, microbial growth enhancing aspects of nanoparticles at optimal concentrations have also been indicated in various studies which involve certain mechanisms such as increased growth rate and cell viability under adverse conditions, induced secretion of environmental stress-combating compounds and enzymes from microbes, provision of high surface area for interaction of beneficial microbial processes, elevation in the production of plant growth-promoting substances and enzymes, enhanced nodule forming ability and protection of the inoculants against desiccation effects and inoculant losses when used as carriers (Ghalamboran et al. 2009; Ghalamboran 2011; Ghalamboran and Ramsden 2012). Dimkpa et al. (2012a) and Haris and Ahmad (2017) indicated a dose-dependent enhancement in siderophore production by PGPRs on exposure to ZnO-NPs, while a similar enhancement was indicated in the IAA production levels on exposure of *Pseudomonas* sp. to CuNPs (Dimkpa et al. 2012b). Studies indicating the increase in exopolysaccharide (EPS) production on exposure to CuNPs, ZnO-NPs and Fe_2O_3 as well as stimulated IAA production on CuO-NPs exposure validate the said impact of nanoparticles on microbes (Oves et al. 2014). Development and subsequent implementation of these formulations would further necessitate the need to check and regulate the impact of nanoparticles on the plant–microbe system and the rhizospheric processes over time (Kah 2015; Dimkpa and Bindraban 2017; Ghorbanpour et al. 2017).

3.4.2 Why Will It Impart Added Benefits?

The hazard linked to the indiscriminate use of mineral nutrients is well known. Also, bio-fertilizers are liable to several inadequacies such as short shelf life and decline in cell numbers, lack of effective carrier, slow rate of action, run-off losses and susceptibility to environmental stresses such as desiccation, salinity and other conditions when applied through conventional methods (Rangaraj et al. 2014; Vejan et al. 2016; Sadeghi et al. 2017; Timmusk et al. 2018).

To overcome these inadequacies in current nutrient management scenarios, nano-biofertilizers can be explored as a potential alternative as these combine the benefits of nano-fertilizers and bio-fertilizers. The benefits can be dichotomized to improve the nutrient use efficiency through reduced application rates, enhanced bioavailability, minimization of environmental losses, and improvement in PGP properties and conditions such as protection of bioinculant from desiccation, better cell viability, reduced cell sedimentation percent in the formulation, increased shelf life and enhanced PGP substance/secondary metabolite synthesis (Rangaraj et al. 2014; Vejan et al. 2016; Duhan et al. 2017; Sadeghi et al. 2017; Timmusk et al. 2018).

Decoding the correct combination of nanoparticle concentration, PGPR and encapsulation technique is though tricky but will enhance the efficacy of the nano-encapsulation process and thereby of the nano-bioformulation itself. With a better view of their action mechanism, it is possible to optimize these mutual interactions for a more regulated release and delivery of formulations at the desired time and site (Vejan et al. 2016; Sadeghi et al. 2017; Timmusk et al. 2018). Nanotechnology being a versatile tool can be used to exploit the great potential of PGPRs in order to facilitate its reproducible implementation in field and sustain the agricultural productivity worldwide (Vejan et al. 2016; Timmusk et al. 2018).

3.4.3 Studies Involving Combinatorial Use of Nano- and Bio-fertilizers

Nano-agriculture aims at attaining more targeted farming with the application of nano-sized particles as fertilizers so as to enhance crop productivity and fertilizer use efficiency through better nutrient availability and uptake (Duhan et al. 2017). As discussed in previous Sects. 3.3.2 and 3.3.3, due to specific properties imparted by their small size, nano-fertilizers are highly efficient for enhancing plant growth activities and crop quality parameters. Further, these fertilizers ensure better protection through reduction in nutrient losses (leaching, run-off), harmful gas emissions and fertilizer wastage (Ghalamboran 2011). Likewise, the nano-based technologies with controlled release mechanisms may also help in decreasing the toxicity conferred by over-application of conventional chemical fertilizers incidentally improving the overall soil health (Vejan et al. 2016). Furthermore, incorporation of the time-tested bio-fertilizer inoculant technology involving the

PGPRs along with nano-fertilizers can provide multiple benefits such as controlled release of the nutrient ion, dual protection of the nutrient and PGPR in encapsulated formulations, improvement in the shelf life and functional efficacy of the microsymbiont due to microbial-priming potential of the co-applied/-encapsulated nano-products (Vejan et al. 2016). Various studies have been undertaken with different crops in order to establish the probable role of augmented application of nano-biofertilizer-based formulations to serve the aim of sustainable crop productivity.

3.4.3.1 Cereal Crops

Cereal crops are considered as the staple food and meet majority of the human food demands globally. Studies aiming at determining the efficacy of nano-bioformulations in improving their productivity have been successfully conducted exhibiting improvement of the crop growth and yield parameters. Enhanced performance of wheat crop in terms of growth and yield was observed on application of nano-biofertilizer (Biozar + Zn, Fe, Mn nanoparticles) (Mardalipour et al. 2014). Application of zinc oxide, iron oxide, CuO and titanium dioxide nanoparticles along with suitable bio-fertilizers were found to boost the PGP action of the biofertilizer besides improving the plant photosynthetic ability and activity of antioxidant enzymes which caused an overall increase in crop growth and yield components (Kheirizadeh Arough et al. 2016; Babaei et al. 2017; Ghooshchi 2017; Timmusk et al. 2018; Anderson et al. 2017). Studies regarding the impact of nano-silica, nano-Ag and calcium phosphate (CaP) NPs in combination with different PGPRs on maize germination and growth displayed sufficient increase in seed germination, growth promotion, root proliferation, improved growth and propagation of beneficial microbes, bio-control activity as well as soil nutrient contents by increased production of phytohormones and improved bioavailability of essential nutrients such as K, Mg, Na, etc respectively. (Karunakaran et al. 2013; Rangaraj et al. 2014; Rane et al. 2015; Khan and Bano 2016).

3.4.3.2 Legume Crops

Legumes serve a major portion of the protein requirement in human diet. Being an integral component of the organic agriculture practices, legume crops can enhance soil fertility for better growth of the subsequent crop besides helping in lowering the requirement of fertilizer inputs and reduction in emission of harmful greenhouse gases (Das and Ghosh 2012; Stagnari et al. 2017). Establishing the positive impact of nano-biofertilizers on legumes can aid in achieving better crop performance in a more economical and bio-safe manner (Farnia and Ghorbani 2014). Investigations aiming at the effect of various nanoparticles such as zinc oxide, magnetite, molybdenum and potassium nanoparticles in conjugation with various bio-fertilizers on leguminous crops such as chickpea, pigeon pea, snap bean and soya bean have depicted their efficacy in improving various traits. Examined nanoparticles and bio-fertilizers were found to enhance the quality and yield parameters, pod production, nodule number and weight, symbiotic systems and biological nitrogen fixation, antioxidant potential of plants, and germination ability, thereby improving the overall physiological state and vegetative growth indices of the crop plants (Ghalamboran 2011; Farnia and Ghorbani 2014; Taran et al. 2014; Kumar et al. 2015; Morsy et al. 2017; Shcherbakova et al. 2017; Jacobson et al. 2018; Khati et al. 2018).

3.4.3.3 Horticultural Crops

Horticultural crops including fruits and vegetables are a major source of essential micronutrients, vitamins and minerals for humans, but are more prone to damage by plant pests and pathogens demanding increased application of pesticides (Imahori 2014). Nano-biofertilizers can be explored as a possible alternative to diminish the uncontrolled use of harmful agrochemicals while improving the crop health and nutritional system. These fertilizers when applied to horticultural crops such as tomato, *Cucurbita*, potato and apple caused a significant increase in fruit and seed yield parameters, better nutritional systems and more vigorous plant growth as compared to control or individual application of nano-fertilizers or bio-fertilizers (Davod et al. 2011; Ajirloo et al. 2015; Razzaghifard et al. 2017; Mohasedat et al. 2018).

3.4.3.4 Forage Crops

Forage crops are a key element for attaining sustainable productivity in agriculture as these crops improve the soil properties by increasing the soil organic matter content, soil fertility and quality, reduce weed development, soil erosion and fertilizer inputs, enhance disease resistance and nutritional value of plants, thereby improving the agricultural and soil output (Capstaff and Miller 2018). Improvement in growth and productivity of forage crops such as red clover and sorghum by enhancing the beneficial traits such as nutritional systems, photosynthetic ability and nitrogen fixation in a sustainable manner can be realized through application of nano-bioformulations (Mir et al. 2015; Moll et al. 2016).

Nanotechnology interventions can provide novel platforms for the production of more refined, efficient and user-friendly products related to plant nutrition or protection management through its integration with formulation technology. These products would then be able to address the impact of current agricultural practices on both human and environmental health while keeping the food security in check (Kah et al. 2018).

3.5 Environmental Safety Issues

The use of nanoproducts for agriculture is hitherto a black-box as unknown risks and possible impacts on human and environmental health on application of nanoparticles are a major concern which may overshadow their benefits (Raliya et al. 2018). While considering the environment and bio-safety aspects of nano-biofertilizer usage, the toxicity and biocompatibility of the nanomaterials must be determined carefully to evaluate the risks associated before their acceptance and use as fertilizers (Cravo-Laureau et al. 2017; Raliya et al. 2018).

Toxicity is not an inherent feature of nanoparticles, but comes into play depending on certain soil–plant system properties besides the application dose of the nanomaterial (Kah et al. 2018). Certain reports indicating the beneficial aspects of nanoparticles are now challenging and contradicting the long-held belief of phytotoxic effects of nanoparticle nutrient elements (Dimkpa and Bindraban 2017).

Evaluation of relative impact of nano-formulations and conventional formulations on environment has not yet been studied, emphasizing the need for work that would compare and evaluate the risks and benefits associated with nano-formulations relative to existing products (Kah et al. 2018). Need of the hour is to develop appropriate protocols and methodologies for proper characterization and assessment of possible impact of nanoparticle use on environment and its components. Considering the variability in type and dose of nanoparticles, growth conditions and plant species, it would be useful to rather keep a check on toxicity and benefits of nanoparticles on a case-by-case basis (Dimkpa and Bindraban 2017).

3.6 Future Prospects

Nano-agriculture is a highly promising field for mitigating fertilizer contamination issues. Therefore these fertilizer formulations may realize the goal of eco-friendly and sustainable agricultural productivity (Kah 2015). Published studies are providing a clarity on various mechanisms of nanoparticle action on environment and its components , though the mechanism of action on biotic components still elusive. Probing the interactions and exchanges between nanoparticles, soil and plant–microbe systems using modern instrumental techniques would allow the understanding of their positive action for the development of efficient nano-bioformulations for field conditions. However, the ecotoxicological risks involved in the use of nanoparticles are not fully characterized yet as most of the toxicological studies performed under laboratory conditions provide no relevance regarding the mobility and uptake of these nanoparticles by living organisms under natural conditions (Kah 2015; Sadeghi et al. 2017; Kah et al. 2018). Therefore, extensive research aimed at deciphering the beneficial as well as the ecotoxic aspects of nanoparticle–soil–plant–microbe system interactions under environmental conditions is necessary for further ensuring developments in nano-agriculture.

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Chapter 4
Role of Metal–Organic Framework (MOF) for Pesticide Sensing

Chansi, Rashi Bhardwaj, Karan Hadwani and Tinku Basu

Abstract Metal–organic framework (MOF) is a three-dimensional porous network built on unique coordination of metal and organic linkers. Few characteristic features such as wide variation in secondary building unit (SBU), abundant functional groups, tuneable porosity, exclusive optical properties, enormous absorption capacity and incredible catalytic properties enable MOF as one of the promising materials in a large number of applications. Starting from removal of pollutants and toxic chemicals from wastewater, catalysing very important and apparently impossible reactions, efficient absorption and separation of gases, hydrogen generation, smart sensing, light emission devices, dialytic membrane to drug delivery, briefly in every aspect of MOF and its composite find major role to play. Strategies adopted to synthesize MOF include conventional technique (solvothermal and non-solvothermal), microwave, electrochemical, sonochemical and mechanochemical. All these techniques have its own advantages and disadvantages and hence silhouette the ultimate properties and applications. Out of wide range of applications, pesticide sensing could be one of the most successful uses of MOF and its composite. The present chapter briefly describes an overview of the applications of MOF and its composites towards pesticide sensing using various types of transducing techniques like optical, electrochemical and chromatography. MOF itself can detect nitro containing organophosphorus (OP) efficiently and selectively via fluorescence imaging.

Keywords Metal–organic framework (MOF) · Absorption · Detection limit · Pesticide detection · Tuneable porosity · Fluorescence quenching

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4.1 Introduction

Metal organic framework (MOF) is a class of cutting-edge materials of porous coordination systems structured by utilizing different metal particles and natural linkers. Unlike other porous materials like metal complex hydrides, actuated carbon and metal complex hydrides, MOF has different topological architecture, abundant functional groups, tuneable porosity and exclusive catalytic properties. Secondary building unit (SBU) of MOF engineering is created on coordination between metal or metal oxides and polytopic regular swaggers or linkers with different functionalities, i.e. bidentate to polydentate, and oversees the final structure. The design of metal particles and different functionalities recommend the final structure formed. Li and colleagues have explained the underlying principle behind the designing of MOF (Li et al. 1999). Figure 4.1 delineates the conceivable states of SBU. The improvement of MOF has conveyed another measurement to the auxiliary delineation of the crystalline materials that are amassed through subatomic bunches, for instance, SBUs in the states of triangles, squares, tetrahedrons and octahedron.

Unique topological architecture, abundant functional groups, tuneable porosity, redox-active metal ions, electron-rich organic ligands, etc., employ exclusive functional properties in MOF such as catalytic activities, filtration, tailor-made template for synthesis, hydrogen generation and sensing. The amalgamation of tuneable porosity and functional group identifies MOF as one of the novel materials in pesticide sensing. The increase in the number of investigations with MOF created noteworthy data for pesticide detection. The strategies used in the design of MOFs play crucial role in point of view of the desired applications and are discussed in this chapter.

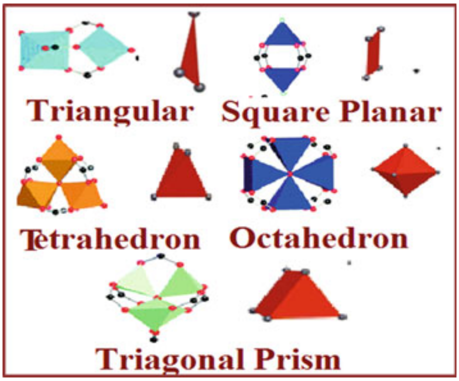

Fig. 4.1 Various secondary building units (SBUs) formed by the coordination between different metal ions and organic linkage for synthesis of varieties of MOF

4.2 Synthesis of MOF

Enormous structural diversity modulates the properties of MOF leading to a wide range of diversified applications. There are various methods for synthesis of MOF including traditional methods, sonochemical, mechanochemical, microwave-assisted, electrochemical technique as illustrated in Fig. 4.2.

4.2.1 Traditional Synthesis Methods

Traditional synthesis methods are categorized as solvothermal and non-solvothermal. Solvothermal implies the use of any solvent at the boiling temperature of the solvent or above in special closed chemical reactors at elevated pressure caused by solvent vapour or produced by a pump, while non-solvothermal process refers to heating below the solvent boiling point in open flasks at atmospheric pressure.

A common scheme involves the choice of the salt (metal source), organic linker and solvent, adjustment of pH and temperature to provide the maximal yield of the target MOF. To form a precipitate, the reaction conditions are maintained to aid the nucleation. The reaction is promoted by use of high temperature and the evaporation of the solvent. The concentration gradient can be achieved by the slow cooling of the solution, solvent layering or slow diffusion of one of the reactants (Stock and Biswas 2011). Many popular MOFs have been synthesized by this method. In particular, mere mixing of solutions without heating produces MOF-5 (Huang et al. 2003; Li et al. 1999), MOF-74, MOF-177 (Tranchemontagne et al. 2008), ZIF-8 (Park et al. 2006). A modified procedure of synthesis of ZIF-8 has also

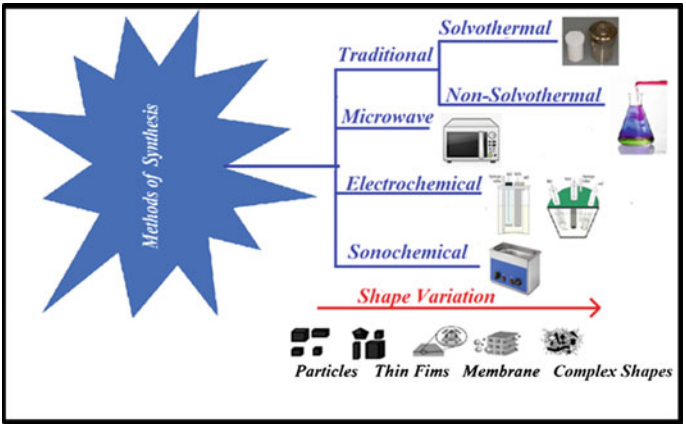

Fig. 4.2 Various methods and mechanisms involved for synthesis of metal–organic framework (MOF)

been reported (Cravillon et al. 2009). Changing the component ratio, the authors have managed to obtain the pure product without heating, excess pressure and ultrasonic or microwave treatment. Another study has reported the synthesis of the layered structure Zn(BDC)(DMF) (H_2O) through a non-solvothermal reaction of zinc nitrate and terephthalic acid and a three-dimensional framework structure of cubic symmetry (Li et al. 1998, 1999). Li and colleagues have synthesized MOF-5 by three approaches: (i) direct mixing of the reactants, (ii) with triethylamine slow addition and (iii) solvothermal synthesis. The Brunauer–Emmett–Teller (BET) surface area of MOF-5 sample synthesized through a solvothermal route was found to be much higher (839 m^2 g^{-1}) than that of the non-solvothermal method (500.8 m^2 g^{-1}) (Li et al. 1999). A similar route via solvothermal synthesis was used to synthesize the MOF UiO-67 with a degradation temperature of 540 °C (one of the highest characteristics of thermal stability among MOF) (Cavka et al. 2008). For synthesis, a solution of zirconium tetrachloride ($ZrCl_4$) and terephthalic acid in DMF was heated at 120 °C for 24 h. A solvothermal method has been used to synthesize different structures with zeolite-like morphology, incorporating zinc (ZIF-1 ± 4, 6 ± 8, 10, 11) or cobalt (ZIF-9) (Park et al. 2006) and imidazole derivatives as linkers. Li et al. (1998) have reported the synthesis of the layered structure Zn (BDC) (DMF) (H_2O) through a non-solvothermal reaction of zinc nitrate and terephthalic acid; a year later, the same team of researchers have synthesized a three-dimensional framework structure of cubic symmetry (Li et al. 1998, 1999).

4.2.2 *Microwave Synthesis*

Microwaves (MWs) are a form of electromagnetic radiation with frequencies between 300 and 300,000 MHz. Out of the two components of radiation, i.e. electrical and magnetic, only the former has usually an effect on synthesis of compounds (Hayes 2002). The maximal MW energy (0.037 kcal/mol) is insufficient for cleavage of chemical bonds in common organic compounds (Hayes 2002). In MW synthesis, effect of electromagnetic radiation on (i) polar particles and (ii) free particles and ions causes prompt warming. The key features of MW-assisted MOF synthesis can be described as (1) increase in speed of crystallization and (2) reduction in size up to a level of nanoscale (3) enhancing purity and (4) specific union of polymorphs. This is because of the immediate warming of the solvents and the higher nucleation rate (Hayes 2002).

A few metal (III) carboxylate-based MOFs (M = Fe, Al, Cr, V, Ce) have been made by microwave-assisted route. The primary MOF made by this method is Cr_MIL-100 in 4 h at 220 °C under MW radiation with 44% yield, which is practically identical with that of chemical combination. The corresponding Fe-based MOF was synthesized in 30 min at 200 °C. The microwave-aided synthesis of nanoscale Cr_MIL-101 has been exhibited in two reports (Jhung et al. 2007; Khan et al. 2011). The prior report shows that the expanding response time enhances size of the nanoparticles from 40–80 to 70–90 nm and turns out to be more homogeneous in size (Jhung et al. 2007). A wide assortment of metal (II) carboxylate-based MOF has been orchestrated by applying MW light. IRMOF-1 and HKUST-1(Hong Kong University of Science and Technology) are among the most contemplated materials. In the most systematic investigation, cubic microcrystals of IRMOF-1 with the length of 2–4 μm were acquired in 9 min at 95 °C in 27% yield. In another report, both size and normality of the cubic microcrystals (4 μm of IRMOF-1) have been diminished up to 1 μm by lessening the convergence of H_2BDC in the beginning arrangement (Ni and Masel 2006). The span of the microcrystals does not change strikingly when the response time has been fluctuated from 25 s to 1 min. In a recent report on IRMOF-1, the MW-assisted method yields higher-quality crystals with better CO_2 adsorption properties, compared to the ambient pressure dynamic synthesis (Lu et al. 2010). Continuous and ordered membranes of IRMOF-1 have been deposited on α-alumina by employing the crystals produced by direct growth as seeds for secondary growth (Yoo et al. 2009). In the MW synthesis of microscale IRMOF-16 $(OH)_2$(20 μm), the crystal quality and porosity of the material improve with an increase in irradiation time (Kim et al. 2011a). The effect of the heating method has been investigated for the synthesis of microscale MOF-177 (5–50 μm) (Seo et al. 2009). Both crystallinity and porosity of the material prepared by MW irradiation were inferior to those obtained by ultrasonic and chemical synthesis. The MW synthesis of HKUST-1 has been systematically investigated in four reports, and the results were compared with other synthesis methods (Seo et al. 2009; Xiang et al. 2010). The MW-assisted synthesis of azolate-based MOF has been described in only a few reports. Rhombic dodecahedral shaped crystals (~20 μm) of the imidazolate-based ZIF-8 have been synthesized at 140 °C in 4 h. The ZIF-8 crystals obtained by MW irradiation show a larger specific surface area compared to the material synthesized under CE heating. Membranes on ZIF-7 and ZIF-8 are also prepared by using MW radiation. In a report of ZIF-8, a dense, crack-free membrane has been deposited on bare titania using the direct growth method (Li et al. 2010). In another report, high-quality membrane of ZIF-7 has been grown on α-alumina by a secondary growth technique (Tonigold et al. 2009).

To produce a seed layer prior to secondary growth, α-alumina has been dip-coated with dispersions containing pre-synthesized nanocrystals and PEI. The pyrazolate-based compound $[Co_4O(BDPB)_3]$ has been synthesized at 155 °C in 2 min under MW radiation (Tonigold et al. 2009). The small, uniform crystals synthesized by MW irradiation exhibit higher catalytic activity in cyclohexene oxidation, compared to the material obtained by CE heating. The MW synthesis of two triazolate-based MOFs, $[Zn_5Cl_4(BBTA)_3]$ and $Zn_5Cl_4(BTDD)_3$ (Denysenko et al. 2011), has been accomplished at 155 °C in 10 and 30 min, respectively. Two mixed-linker MOFs were prepared under MW irradiation. The microwave sample of $[Zn_2(NDC)_2(DPNI)]$ shows slightly lower capacity for CO_2 and CH_4 compared to the sample prepared by CE heating, but it has much higher selectivity of CO over CH_4 (Bae et al. 2008). In another work, one of the polymorphs of the pillared layered $[Ni_2(BDC)_2(DABCO)]$ framework has been synthesized by employing a high-throughput MW-assisted method (Maniam and Stock 2011). Combination of MW irradiation, low overall concentration, stirring of the reaction mixtures and an excess of DABCO (1,4-diazabicyclo [2.2.2] octane) yields the phase-pure polymorph $[Ni_2(BDC)_2(DABCO)]$ $(DMF)_4$ $(H_2O_4)]$.

4.2.3 Electrochemical Synthesis

Electrochemical MOF film deposition on conducting surface is an enabling technology for industrially relevant application. Two fundamentally different electrochemical approaches for MOF deposition are described as anodic deposition and cathodic deposition, respectively. In anodic deposition, MOF film formation occurs on a respective metal anode contacted with a ligand solution as a result of the release of a critical concentration of metal ions by anodic dissolution (Mueller et al. 2007). In cathodic deposition, a solution containing a ligand, metal ions and a so-called probase is contacted with a cathodic surface. Film formation on cathode occurs due to an increase in pH near the cathodic surface, where electrochemical reduction of the probase results in local base generation and subsequent ligand deprotonation, inducing MOF formation (Mueller et al. 2007).

The electrochemical synthesis of MOF was first reported in 2005 by researchers at BASF to synthesize MOF (HKUST-1) (Mueller et al. 2006). As the dissolving anode, copper sheets of 5 mm thick were used. The sheets were dipped in a solution of benzene-1,3,5-tricarboxylic acid (H_3BTC) in methanol together with copper cathodes, acrylic or maleic esters that preferentially reduce reactions. This makes it possible to avoid the formation of anions during reaction and to initiate a continuous process, which is essential for going to the production of relatively large amounts of MOFs. To date, the electrochemical formation of microcrystalline powders and films is reported. Researchers from BASF have performed the pioneering work and have established synthesis procedures for some Cu- and Zn-based MOF (Mueller et al. 2007). In their study, various combinations of anode materials (Zn, Cu, Mg, Co) and linkers [1,3,5-H_3BTC, 1,2,3-H_3BTC, H_2BDC and $H_3BDC(OH)_2$] as well as different experimental set-ups are mentioned which also allow the up-scaling of the synthesis. From these combinations, four Cu- or Zn-containing compounds with high porosity were obtained. The HKUST-1 product is tested for its use in gas purification, i.e. removal of tetrahydrothiophene from natural gas, H_2 storage and the separation of Kr-Xe mixtures (Mueller et al. 2006). This work is further extended to the chemistry of ZIF (Khazalpour et al. 2015). Synthesis procedures led to the formation of $[Zn(MIm)_2]$ and $[Zn(BIm)_2]$ showing specific surfaces of 1746 and 465 m^2/g, respectively. Studies by other groups have exclusively focused on the electrochemical synthesis of HKUST-1. This method produces both powders and films. For example, a thin layer of HKUST-1 is electrochemically deposited on copper mesh used as anode (Van Assche et al. 2012). The cathodic electrodeposition leading to the formation of biphasic metal–organic framework thin films at room temperature from single deposition baths using potential bias as the main user input has been reported. Depending on the applied potential, selectively deposition of two different phases as either bulk mixtures or bilayer films (Wade et al. 2013).

4.2.4 Mechanochemical Synthesis

In mechanochemical synthesis, the mechanical breakage of intramolecular bonds followed by a chemical transformation takes place. Its use for the synthesis of porous MOF was first reported in 2006 (Pichon et al. 2006). The mechanochemical synthesis of HKUST-1 has been thoroughly investigated. Starting from a stoichiometric ratio of Cu^{2+} to H_3BTC (3:2), solvent-free grinding as well as LAG results in the desired product. Cu salts, grinding conditions (time and frequency), presence/absence of a solvent and nature of the solvent (DMF, methanol, H_2O/ ethanol) have been studied. Imidazolate (Im)-based compounds have also been synthesized by mechanochemical synthesis (Fujii et al. 2010; Willans et al. 2011), while the reaction of imidazole with ZnO or zinc chloride led only to non-porous $Zn(Im_2)$. Combining of ZnO in the presence of DMF yields quantitatively ZIF-4 and ZIF-8 in the presence of hydoxyimidazole (HIm) and hydroxymethanol imidazole (HMIm), respectively. The synthesis of ZIF is facilitated in the presence of the ammonium ions. Zn-based mixed-linker MOF with the composition $[M_2(\text{dicarboxylate})2(\text{diamine})]$ exhibits pillared layered structures; i.e. 2D metal carboxylate sheets containing inorganic paddle wheel units are pillared by ditopic amines. Starting from a mixture of zinc acetate, fumaric acid, the synthesis is repeated in the absence of a solvent, and the interpenetrated structure is refined using Rietveld methods (Friščić et al. 2010).

Mechanochemical synthesis and grinding-induced transformation of three different non-porous solvated Zn terephthalates are demonstrated, showing the liability of the compounds under grinding conditions. These compounds are also used as starting materials to synthesize pillared layered MOF. Direct mechanochemical synthesis starting from ZnO or $Zn_5(CO_3)_2(OH)_6$ or direct immersion of the non-porous Zn terephthalates in a solvent containing carboxylate is generally not successful (Yuan et al. 2010). Nevertheless, the pillared layered MOF based on a square grid is preferentially obtained using KNO_3, NH_4NO_3, Na_2SO_4. $(NH_4)_2$ SO_4 or K_2SO_4, quantitatively on a hexagonal (kagome) grid. HKUST-1 has been synthesized by the mechanochemical method. Cu-BTC (HKUST-1) was prepared by the ball milling possess a very high surface area of 1713 m^2/g. The structure contains copper dimeric paddle wheel unit making it a highly porous material (Klimakow et al. 2010). The molecules are removed using the one-step pot synthesis method with gaseous by-product as a driving force.

4.2.5 Sonochemical Synthesis

The effect of ultrasound on fluid and colloid frameworks is predominantly caused by cavitation. This is a method of vapour arrangement and air discharge caused by diminishing weight in a fluid as a high-force acoustic wave proliferates through it. Hypothetically, a fluid begins bubbling when the weight in a few areas of the stream is diminished to its immersed vapour weight. Be that as it may, diminishing in weight prompts the arrival of broke-down air from fluid and development of gas voids, depressions. Sonication has been utilized for combination of a MOF (to be specific, $Zn_3(BTC)_2$) in 2008 (Son et al. 2008). Zinc acetic acid derivation and H_3BTC are blended in 20% ethanol and subjected to sonication for a couple of minutes (up to 90 min). They can decrease the synthesis time of MOF-5 from 24 h (customary warming) to 75 min utilizing sonication. A mixture of zinc nitrate and terephthalic acid in 1-methyl-2-pyrrolidone in a nitrogen gas was subjected to sonication for 10 ± 75 min to prepare MOF-5 within 8 min of sonication. Combination of Cu-BTC MOF has been refined at a recurrence of 40 kHz inside 5–60 min with a yield of 62.6–85.1%. Several synthetic routes have been investigated for the synthesis of Fe MIL-88A with the goal to obtain monodisperse nanoparticles in a high yield. Different parameters, such as temperature time (0.5, 1, 1.5 and 2 h), concentration and pH (addition of acetic acid or NaOH), have been evaluated by an ultrasonic technique. The systematic study shows that the particle size increases as a function of concentration, reaction time, and temperature and crystallization rate increase with pH. Thus, by working with addition of acetic acid under dilute conditions, monodisperse small particles (<200 nm) were obtained. Unfortunately, the yield was found to be lower than 5% (Chalati et al. 2011). The most recent article demonstrates the unexpected influence of the ultrasonic power level on the product formation. Two examples of interpenetrated and non-interpenetrated structures, i.e. PCN-6/PCN-60 and IRMOF-9/IRMOF-10, were presented. While at lower power levels the non-interpenetrated structure is obtained, intermediate power levels led to mixtures and higher power levels to phase-pure interpenetrated structure of the corresponding MOF (Kim et al. 2011b).

4.3 Applications of MOF for Pesticide Sensing

MOF being an isoreticular structure can offer diversified application including gas separation, drug delivery, sensing, optical devices, source of light emission and catalysis (Furukawa et al. 2010; Zhou et al. 2012). One of the potent applications of MOF is separation of rare gases by adsorption from mixtures (Czaja et al. 2009). The unique physicochemical properties like high porosity, high specific surface areas and varied pore sizes and topologies of MOFs make them promising materials in sensing applications. The shape, size, selectivity, attainable bulk volume and porous architectonics of MOF materials tune catalytic properties; diverse structural architectures, charge transfer from ligand to metal and tunable luminescence direct the MOFs as promising candidates for light-emitting display devices and lighting applications for improved sensing applications. Inspired by the activated carbon, carbon nanotubes, zeolites, etc., MOF is extensively investigated as gas storage devices, due to the scope of designing of supple frameworks and varied geometries. MOF possesses essential features such as drug loading ability, biocompatibility, biodegradability and adaptable functionality to make them potent candidate in targeted drug delivery, tissue engineering and sensing in biomedical field.

As pesticides are non-biodegradable in nature, they are known to amalgamate and carry through in the environment for a very long period of time. Recent studies have proclaimed that leakage in pipes and underground storage depots, rubbish heaps, spills and run-offs into surface water are the dominant culprits for the aggregation of pesticides in the food chain, causing damage to human health. The detection of pesticides and their remnants in the environment has traditionally been carried out via conventional analytical advances such as gas and high-performance liquid chromatography. Between a myriad of accessible nanomaterial systems, MOFs have come forth as a dependable and conceivable solution for selective and sensitive detection of pesticide, based on biosensing, chemosensing and electrochemical sensing approaches, as potent and novel sensors. Deep and colleagues have marked MOF as a novel scaffold for direct sensing of nitro containing organophosphate pesticide via fluorescence quenching (Deep et al. 2015). Apart from these, various mechanisms are involved for the detection of the pesticides along with the MOF aided for the sensitive analysis. MOF-based sensing advances used for the detection of pesticides are discussed in detail in further section (Fig. 4.3).

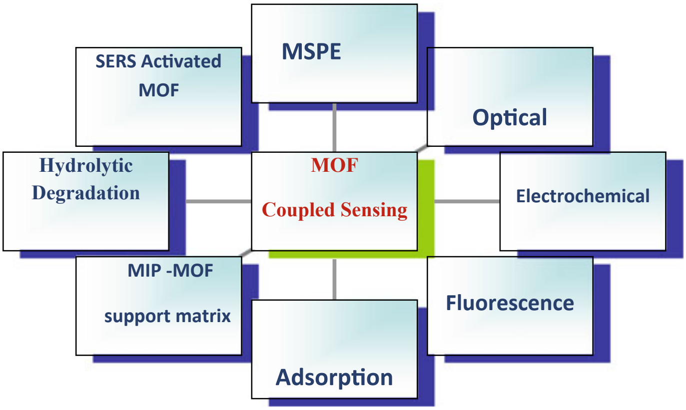

Fig. 4.3 Various sensing techniques coupled with MOF for pesticide sensing

4.3.1 Magnetic Solid-Phase Extraction (MSPE) Extracted Magnetic MOF Composites for Pesticide Detection

MOF functions as a reservoir for the absorption of analyte; hence, its adsorptive capability is harnessed for the detection of pesticides. High-performance liquid chromatography (HPLC) coupled with MOF has been explored. MSPE of heterocyclic pesticides, namely triadimefon, chlorfenapyr, carbendazim and fenpyroximate, is done by the amalgamation of magnetic MOF formed by the modification of the synthesized MOF-5. MSPE copulated with the HPLC displays exceptional linearity range of 0.3–500.0 μg/L for carbendazim and triadimefon, and 0.1–500.0 μg/L for chlorfenapyr and fenpyroximate, with correlation coefficients (r) greater than 0.9992. High sensitivity with LOD and LOQ ranging from 0.04–0.11 μg/L to 0.13–0.35 μg/L was documented. The method has been employed for the detection of the pesticide in Yellow River water sample with 80.2 and 108.3% detection limit, respectively (Ma et al. 2018).

A nanocomposite (TMU-4/PES) has been prepared using zinc-based MOF (TMU-4) and polyether sulphone as a unique coating for the detection of pesticides. The nanocomposite represents a novel fibre coating for headspace solid-phase microextraction of organophosphorus pesticides (OPPs) from environmental water and soil samples. The synergistic effects of the high surface area and unique porous structure of TMU-4 as well as the rich π electron stacking and mechanical attributes of the PES polymer result in a high affinity of the composite for OP. The preparation of the coating was simple, and the coated fibre was highly stable and reusable and can be used in about 100 consecutive extractions/desorption cycles. The limits of detection were in the 5–8 ng/mL range for the OP diazinon, fenitrothion, malathion and chlorpyrifos. The method has been applied to the trace determination of OPPs in (spiked) water and soil samples where it shows good recovery (88–108%) and satisfactory reproducibility (5.9–10.1%) (Bashtani et al. 2018). MOF $[(La_{0.9}Sm_{0.1})_2(DPA)_3(H_2O)_3]\infty$ was synthetized by matrix solid-phase dispersion (Barreto et al. 2010) procedure for extraction of atrazine, bifenthrin, bromuconazole, clofentezine, fenbuconazole, flumetralin, procymidone and pirimicarb, from peppers, with analysis using gas chromatography with mass spectrometry in the selected ion monitoring mode. Detection and quantification limits range from 16.0 to 67.0 μg/kg and from 50.0 to 200.0 μg/Kg, respectively, for the different pesticides studied. The developed method was approved for the real samples. Magnetic porous carbon material was synthesized from bimetallic MOF (Liu et al. 2017). This carbon element was used in magnetic solid-phase extraction of the organochlorine pesticide. High extraction and good sensitivity were achieved through this method displayed good linearity ($r > 0.99$) within the concentration range of 2–500 ng/L. Low limits of detection [0.39–0.70 ng/L, low signal-to-noise ratio (3:1)] and limits of quantification (1.45–2.0 ng/L), as well as good precision (relative standard deviation <10%), were also obtained.

4.3.2 Gas Chromatography Coupled with MOF for Pesticide Detection

A high surface area nanoporous carbon (NPC) has been successfully synthesized by using the MOF ZIF-90 as both the template and the precursor together with furfuryl alcohol as a secondary carbon source (Zhang et al. 2014). The prepared ZIF-90-templated NPC (ZIF-90-NPC) was coated onto a stainless-steel wire by a simple physical adhesion approach to prepare solid-phase microextraction (SPME) fibre. By coupling the ZIF-90-NPC-coated fibre-based SPME with gas chromatography-microelectron capture detection (GC-μECD), the developed method had given a large enhancement factor (984–2869), low limit of detection (0.1–0.5 ng g^{-1}) and good linearity (0.3–50 ng g^{-1}) for the determination of some pyrethroid pesticides (bifenthrin, fenpropathrin, cyhalothrin, permethrin, cyfluthrin, flucythrinate, fenvalerate and deltamethrin) from different fruits and vegetables. The relative standard deviations (RSDs) for six replicate extractions of the pyrethroids by the ZIF-90-NPC-coated fibre range from 4.3 to 8.0%. The recoveries of the spiked pyrethroids (5 ng g^{-1} and 20 ng g^{-1}) from fruit and vegetable samples are in the range of 88.0–104.0% and 86.0–103.5% with the RSDs ranging from 4.8 to 12.9 and 5.0–10.8%, respectively. Besides, the ZIF-90-NPC-coated fibre is stable enough for 100 extraction cycles without a significant loss of extraction efficiency. The method is successfully applied to the determination of the pyrethroids in fruit and vegetable samples.

Magnetic MOF (MIL-101) has been prepared and used as magnetic solid-phase extraction (MSPE) adsorbents for preconcentration of four kinds of pyrazole/pyrrole pesticides (flusilazole, fipronil, chlorfenapyr and fenpyroximate) in environmental water samples, followed by high-performance liquid chromatography-diode array detector (HPLC-DAD) determination (Ma et al. 2016). MOF was used as a support material for the synthesis of various nanoparticles. MIL-101 support is used for synthesis of molecularly imprinted polymer (MIP) nanoparticles. These particles are well dispersed over the surface with wide surface area. MIL@MIP interface works as a modified surface for the detection of metolcarb pesticide. By using an external magnet, pesticide can be separated by this Fe_3O_4@SiO_2–MIL-101 without any external device.

An active magnetic MOF hybrid material is prepared using a novel in situ solvothermal method in the presence of magnetite (Fe_3O_4) particles that holds much promise for large-scale synthesis. MIL-101(Fe), an iron terephthalate with pore structure and high resistance to water and common solvents, is functionalized as a model with superparamagnetic qualities, using Fe_3O_4. The electrostatic interaction between Fe_3O_4 and metal ions is thereby used to chemically stabilize magnetic nanoparticles, and thus MOF crystals are uniformly enclosed by Fe_3O_4 to form a homogeneous magnetic product identified as a Fe_3O_4/MIL composite (Zhang et al. 2014). This hybrid material with magnetic susceptibility but with the lowest possible loading amount of Fe_3O_4 is examined, and its potential application for magnetic solid-phase extraction of six organophosphorus pesticides (OPPs) from human hair and urine samples, followed by gas chromatography analysis, is assessed. The effect of various parameters including solution ionic strength, desorption solvent, extraction time and desorption time is investigated in sequence. Under optimized conditions, this method displays low detection limits (0.21–2.28 ng/mL), wide linearity and good precision (1.8–8.7% for intra-day and 2.9–9.4% for inter-day). The matrix interference produced by hair or urine can be effectively eliminated using this method, and satisfactory recoveries of the spiked samples are 76.8–94.5% and 74.9–92.1%, respectively, indicating that the Fe_3O_4/MIL-101 sorbents are feasible for the analysis of trace analytes from biological samples.

4.3.3 MOF Coupled Adsorption for Pesticide Detection

A novel magnetic MOF has been synthesized using a Fe_3O_4–GO–β-CD nanocomposite as the magnetic core (Liu et al. 2017), and the support had been used for the rapid adsorption and removal of neonicotinoid insecticides from tap water samples. The developed M-MOF had high super-paramagnetism and a large BET surface area, which enabled rapid M-MOF separation from water samples. Besides, the hydrophobic inner cavities, supramolecular recognition of Fe_4O_3–GO–β-CD, significantly improve the adsorption capacity and rate of M-MOFs for neonicotinoid insecticides. Adsorption experiments show that M-MOF possesses high adsorption capacity for neonicotinoid insecticides. Spiked tap water samples were treated with M-MOF to remove neonicotinoid insecticides. The results suggested that the developed M-MOF was a simple and effective potential adsorbent for the removal of neonicotinoid insecticides from environmental waters.

High surface area is as an aided advantage for the detection of pesticide. Highly luminescent MOF with high surface area of 4073.9 m^2/g exhibits an excellent adsorption ability towards rapid sensing of methyl parathion (Liu et al. 2017). This was an excellent example of luminescent MOF for sensing for methyl parathion with a very wide linear detection range from 1.0 μg/L to 10 mg/kg, and low limit of detection 0.12 μg/kg (0.456 nM) via fluorescent quenching. The quenching effect of methyl parathion is attributed to the electron-rich chemical group of nitroaromatics which might lead to photo-induced electron transfer. The fluorescent method is reliably useful for the determination of methyl parathion in spiked irrigation water with satisfactory results, which suggested its potential for rapid detection of pesticides in food and environmental sample.

A zinc(II) benzenetricarboxylate (Zn-BTC)-based MOF with chrysanthemum-like structure has been used for the absorption of pesticides from real water samples (Wang et al. 2017). The MOF used in dispersive solid-phase extraction of six aromatic pesticides from various wastewater samples prior to their quantification by HPLC was optimized. Under the optimal conditions of extraction time, temperature, amount of adsorbent and oscillation rate, the method has relative standard deviations (RSDs) of 6.1–10.1% and good linearity (correlation coefficients higher than

0.9974). The LODs and LOQs for seven pesticides were found to be 0.20–1.60 μg L^{-1} and 0.66–5.28 μg L^{-1}, respectively. The RSDs within batch extraction were 1.6–9.5% and 3.9–12%.

Magnetic porous carbon material derived from a bimetallic MOF has been explored as an adsorbent for magnetic solid-phase extraction of organochlorine pesticides (OCPs). The synthesized porous carbon possesses a high specific surface area and magnetization saturation. The OCP in the samples is quantified using gas chromatography coupled with a triple quadrupole mass spectrometer. The experimental parameters, including the desorption solvent, amount of adsorbent, extraction time, extraction temperature and ionic strength of the solution, are optimized. Under optimal conditions, the developed method displays good linearity ($r > 0.99$) within the concentration range of 2–500 ng/L. Low limits of detection (0.39–0.70 ng/L, signal-to-noise ratio = 3:1) and limits of quantification (1.45–2.0 ng/L, signal-to-noise ratio = 10:1) as well as good precision (relative standard deviation <10%) were also achieved. The developed method had been applied in the analysis of OCPs in drinking and environmental water samples.

The removal of two representative organophosphate pesticides, glyphosate (GP) and glufosinate (GF), has been examined by the exceptionally stable Zr-based MOF known as UiO-67 (Zhu et al. 2014). The abundant Zr-OH groups, resulting from the missing-linker-induced terminal hydroxyl groups and the inherent bridging ones in Zr-O clusters of UiO-67 particles, served as natural anchorages for efficient GP and GF capture in relation to their high affinity towards phosphoric groups in OPs. The correlation between the most significant parameters such as contact time, OPs concentration, adsorbent dose, pH as well as ionic strength with the adsorption capacities was optimized, and the effects of these parameters on the removal efficiency of GP and GF from the polluted aqueous solution were investigated. The adsorption of GP on UiO-67 was found to be faster than that of GF, and a pseudo-second-order rate equation effectively described the uptake kinetics. Langmuir model exhibited a better fit to adsorption isotherm than Freundlich model. The strong affinity and adequate pore size, the adsorption capacities in UiO-67 approaches as high as 3.18 mmol (537 mg)/g for GP and 1.98 mmol (360 mg)/g for GF, which were much higher than those of many other reported adsorbents. The excellent adsorption characteristics of the current adsorbents towards OPs were preserved in a wide pH window and high concentration of the background electrolytes. These prefigure the promising potentials of UiO-67 as novel adsorbent for the efficient removal of OPs from aqueous solution.

Pesticide removal from wastewater is a noteworthy general benefit to salvage the human life from various types of pollutions present around us. MOF has been established as an exceptional material for organophosphate pesticide pollution remediation. A facile method has been used to functionalize cotton fabric by assembly with Cu-BTC MOFs (Abdelhameed et al. 2016). The so-prepared Cu-BTC@cotton composite has been characterized by X-ray diffraction, infrared spectroscopy, elemental analysis and electron microscope. Cu-BTC has been successfully bonded with cotton fabrics through interaction between Cu and cellulose functional groups. Adsorption of ethion as organophosphorus insecticide onto

Cu-BTC@cotton composite had been systematically studied. Binding sites of composite represented in cellulose functional groups and Cu of MOF are both linked with ethion via sulphur. The equilibrium adsorption isotherm proves that the adsorption of ethion insecticides fitted well to Langmuir model. The maximum sorption capacity of Cu-BTC@cotton composite had reached to 182 mg/g, and the removal per cent of ethion exceeded 97%. Furthermore, Cu-BTC@cotton composite was very stable and can be easily recycled using a simple organic solvent. After five times of recycling, the adsorption efficiency of Cu-BTC@cotton composite is still very good and surpassed 85%. Hence, Cu-BTC@cotton is a perfect sorbent to remove insecticides from wastewater with an excellent efficiency (Abdelhameed et al. 2016).

Immobilization of Cu-BTC metal–organic framework (MOF-199) particles by enmeshing them in non-woven polyacrylonitrile (PAN) nanofibres (Abdelhameed et al. 2016) creates a fibrous membrane with the potential ability to remove chemical warfare agents or pesticides from solution. These membranes were shown to effectively adsorb methyl parathion, an organophosphate pesticide. Based on solubility theory and experimental results, partitioning was found to be the main mechanism of removal. After 2 h, the PAN/MOF-199 membrane removes 88% more methyl parathion than the unmodified PAN membranes and 62% as much as the MOF-199 crystal powder. Since the MOF particles were enmeshed in the PAN fibre mats, the MOF particles were in a workable and flexible substrate. Potential applications of these functionalized fibrous membranes include protective clothing for agricultural workers or military personnel as well as filtration media.

4.3.4 Detection of Pesticide by Optical Method

Luminescence and high surface area are two important attributes of MOF which enable them as a potential platform for optical sensing (Singha et al. 2017). MOF-5 with high surface area of 4073.9 m^2/g demonstrated an excellent adsorption ability and sensing performance by fluorescent quenching in rapid detection of methyl parathion within wide linear detection range from 1.0 μg/L to 10 mg/kg, and low limit of detection 0.12 μg/kg (0.456 nM) (Xu et al. 2018). This low detection limit was much lower than the maximum residue limits (MRLs) in the European Union pesticide database (0.01 mg/kg for fruits and vegetables, and 0.02 mg/kg for tree nuts). The quenching effect of methyl parathion arises from electron-rich chemical group of nitroaromatics which might lead to photo-induced electron transfer (PET) and has been efficaciously applied for testing of methyl parathion in spiked irrigation water suggesting its potential for rapid detection of pesticides in food and environmental sample.

A novel LMOF was designed through the incorporation of a molecular fluorophore and an anthracene-based colinker into a Zn-based structure (Rudd et al. 2018). The compound crystallized in a body-centred orthorhombic crystal system (space group: *Imma*) as a three-dimensional porous network of (LMOF-271) is classified as a two-nodal, (4,6)-c net (sqc124 type) with two stoichiometries. LMOF-271 contained two-dimensional sheets of paddle-wheel-type Zn-SBUs interconnected by anthracene-based colinkers, with tetradentate chromophores linking the nets together. Pristine LMOF-271 emits blue light (475 nm) upon UV excitation (365 nm), and selectively detects the toxic environmental contaminant carbon tetrachloride over similar volatile organic solvents, namely dichloromethane and chloroform. This work was the first study that used a LMOF to selectively and effectively detect carbon tetrachloride via luminescence signal change with a high KSV value of 48,903/M and a detection limit of 22 ppb.

Another MOF called $Cd_{2.5}(PDA)(tz)_3$ where PDA is 1,4-Phenylenediacetate and 1,2,4-triazolate1 has been amalgamated by solvothermal method (Singha et al. 2017). The structural and morphological characterization confirmed a cage-like structure connecting three dimensions with three distinctive types of Cd^{2+} ions (square pyramidal, trigonal antiprism and octahedral geometries). Photoluminescence studies of the above MOF in aqueous medium show emission at 290 nm upon excitation at 225 nm which was successively utilized for selective and sensitive detection of azinphos-methyl pesticide in aqueous medium through luminescence quenching. It can detect azinphos-methyl with a detection limit of 16 ppb, and its sensitivity remains unchanged in the presence of other pesticides.

A novel pillared-layered entangled LMOF known as $[Zn_2(bpdc)_2(BPyTPE)]$ (1) where (BPyTPE is (*E*)-1,2—diphenyl-1,2-bis(4-(pyridin-4-yl) phenyl)ethene) exhibits strong blue-green emission with an excellent fluorescence quantum yield of 99% and provides a facile and reversible method to sensitively and quantitatively detect trace amount pesticide of 2,6—dichloro-4-nitroaniline (Tao et al. 2017). A family of thiophene-based MOF, $[Zn(L)(BBI)\cdot(H_2O)_2]$ (BBI = 1,1′-(1,4-butanediyl)bis(imidazole)) and $[Cd(L)(TPOM)0.75]\cdot xS$ (TPOM = tetrakis(4-pyridyloxymethylene) methane (*S* represents non-coordinated solvent molecules) have been constructed by employing a new linear thiophene-functionalized dicarboxylic acid (benzo-(1,2;4,5)-bis(thiophene-2′-carboxylic acid, H_2L) to assemble with d_{10} ions in the presence of flexible ancillary ligand under solvothermal conditions, which exhibit diverse structures (Tao et al. 2017). Most strikingly, both compounds $[Zn(L)(BBI)\cdot(H_2O)_2]$ and $[Cd(L)(TPOM)0.75]\cdot xS$ can be treated as an efficient luminescent sensory materials for highly selective and sensitive to environmental contaminants, especially for Hg(II), Cu(II), Cr(VI) and salicylaldehyde, and yet remain unaffected by other molecules that may coexist. Furthermore, this was the first report on the MOF-based sensors capable of recyclable detection of Hg (II), Cr (VI) and salicylaldehyde so far. In addition, compound [Cd(L)(TPOM)0.75] is one of the rare examples of high-performance MOFs trapping 2,4-dichlorophenol from the wasted methanol solution (Tao et al. 2017).

Sensitive photo-electrochemical (PEC) sensor for the determination of the herbicide clethodim was constructed using amino-MIL-125/TiO_2 (MIL stands for Materials from Institute Lavoisier) (Jin et al. 2015). The amino-MIL-125/TiO_2 was synthesized by an uncomplicated one-step solvothermal reaction and deposited on a glassy carbon electrode where it displays good photo-electrocatalytic activity. In the sensing process, amino-MIL-125/TiO_2 was illuminated by visible light to produce electrons. These excited electrons were delivered to the glassy carbon electrode, leaving positively charged holes (h+) on the surface of the amino-MIL-125/TiO_2. The holes react with OH to generate hydroxyl radicals (OH). Clethodim rapidly attacks the hydroxyl radicals and improves the efficiency of charge separation, leading to an enhanced photocurrent. Under the optimal experimental conditions, this photo-electrochemical method enables clethodim to be quantified in the concentration range from 0.2 to 25 μmol L^{-1}, with a detection limit (3 S/N) of 10 nmol L^{-1}. The assay was extrapolated to determine clethodim in soil samples, and results were in congruent with data obtained by liquid chromatography/mass spectrometry (LCMS).

A luminescent nanocrystal LNMOF1 of $[Cd(atc)(H_2O)_2]n$ developed by the reaction of Cd(II) ions with the sodium salt of H_2atc(2-aminoterephthalic acid) in aqueous solution exhibits fluorescence attributes at an excitation wavelength of ¼ 340 nm and emission wavelength of ¼ 436 nm and had been used for the sensing of the nitroaromatic-containing nitro OP such as parathion, methyl parathion, paraoxon and fenitrothion (Kumar et al. 2014). It was possible to detect the above four OPs separately in the concentration range of 1–500 ppb with a detection limit of 1 ppb. Interestingly, their mixture also supports the above characteristic data. The proposed method for the sensing of nitro OP is also selective towards another OP such as malathion, dichlorvos and monocrotophos.

The treatment of Cd(II) ion with the sodium salt of H_2atc (H_2atc= 2-aminoterephthalic acid) in aqueous solution facilely yielded crystal nanorods of MOF at room temperature (Wang et al. 2012). The NMOF of $[Cd(atc)(H_2O)_2]$ n (NMOF1) had been realized for the straightforward and highly sensitive sensing of nitroaromatic compounds in ethanol solution by the fluorescence quenching and fluorescence titration experiments.

4.3.5 Electrochemical Method of Pesticide Detection

MOF-derived nanomaterials in porous carbon possess excellent conductivity and distinctive microstructure, which could improve the analysis of performance of biosensors by loading large amounts of enzymes and accelerating electron transfer. Fe_2O_3@C has been derived from annealing of Fe-1,3,5-benzenetricarboxylate (Wei et al. 2018). However, two biosensors based on Fe_2O_3@C and ionic liquid (IL)/ nafion (NF) for sensing analysis of H_2O_2 and paraoxon via immobilization myohemoglobin (Mb) and acetylcholinesterase (AChE) on carbon paste electrodes (CPEs), respectively, demonstrated excellent electrochemical performance towards H_2O_2 and paraoxon with the detection limit as low as 1.7×10^{-7} M and 1.2×10^{-14} M, respectively. Especially, present NF/AChE/NF-Fe_2O_3@C/CPE enhances sensitivity for the determination of paraoxon. The results indicated that Fe_2O_3@C was a promising electrode material in the development of multifarious biosensor fabrication with sensitive detection of target molecules other than H_2O_2 and paraoxon.

The deposition of thin films of a silica oxide (SiO_2)-modified copper based—MOF, $Cu_3(BTC)_2$ [$Cu_3(BTC)_2@SiO_2$, BTC = benzene-1,3,5-tricarboxylic acid]—on a conducting substrate of NH_2—BDC [NH_2—BDC = 2-aminobenzene-1,4-dicarboxylic acid]-doped polyaniline (PANI) conjugated with anti-atrazine antibodies had been created as a immunosensing platform for the conductometric sensing of atrazine (Bhardwaj et al. 2015). The detection of atrazine was accomplished with an excellent sensor sensitivity (-LOD = 0.01 nM) and specificity in the presence of a variety of pesticides (e.g. endosulphan, parathion, paraoxon, malathion and monocrotophos).

The assembly and pesticide sensing application of a NMOF [$Cd(atc)(H_2O)_2$]n (‘atc’¼2-aminoterephthalic acid) have been achieved by sequential dipping of a 2-aminobenzylamine (2-ABA)-modified indium tin oxide (ITO) slide in organic linker ‘atc’ and metal ion ‘Cd_2þ’ solutions. The presence of pendent –COOH functional groups on the amassed NMOF film conjugated with anti-parathion antibody has been explored for the electrochemical impedance spectroscopy (EIS)-based analysis of parathion in the concentration range of 0.1–20 ng/mL. The proposed detection was found to be specific with respect to other OP compounds, e.g. malathion, paraoxon, fenitrothion, monocrotophos and dichlorovos. The proposed sensor showed the detection limit of 0.1 ng/mL and was applicable for analysis of parathion in a rice sample. The sensor’s performance was validated by comparting the obtained results with gas chromatographic data.

A new conjugated metal–organic framework based on 2,20,4,40-biphenyltetracarboxylic acid with a uninodal five connected hexagonal boron nitride nanotube (bnn) nets had been synthesized, which represents the first example of metal–organic frameworks capable of adsorbing a trace level of organophosphate pesticide for efficient detection via stripping voltametric analysis (Wen et al. 2010). A detection limit of 0.006 μg/mL was achieved.

4.3.6 *SERS Active Metal–Organic Framework with Embedded Gold Nanoparticles*

Surface-enhanced Raman scattering (SERS) has been widely used in the detection of targets, strongly dominated by the interaction and the distance between targets and nanoparticles (Cao et al. 2017). In one study, Uio-66 and Uio-67 MOFs were large scale synthesized by water bath method, and MOFs embedded with gold nanoparticles (Au NPs) for SERS enhancement were successfully fabricated by impregnation strategy. The synthesized AuNPs/MOF-199, AuNPs/Uio-66 and AuNPs/Uio-67 composites with LSPR properties and high adsorption capability of MOF to preconcentrate analytes close to the surface of Au NPs showed perfect SERS activity. The limits of detection with the signal/noise ratio higher than 3 at characteristic peak 632 cm^{-1} were 0.02, 0.009 and 0.02 μM for acetamiprid, respectively. Most interestingly, the AuNPs/MOF-199 composites of long tube sheet perform excellent SERS activity and provided new route to detect pesticide with SERS technology with high sensitivity, stability and reproducibility.

4.3.7 Hydrolytic Degradation of Pesticide for Detection

The water-stable mesoporous channel-type zirconium MOF PCN-128y was shown to be capable of encapsulating OPAA with a high loading (Li et al. 2016). This size-matching encapsulation process was performed rapidly under mild conditions and required no prior chemical modification of the protein of interest. More importantly, following OPAA uptake by the large (mesoporous) channels of PCN-128y, the smaller channels (microporous) of the hierarchically structured host material remained open and available as conduits for reactant and product diffusion to and from the active sites of the encapsulated enzymes. In addition, PCN128y excels at stabilizing the enzyme at high temperature and in dry form, whereas the free enzyme degrades rapidly under these conditions. These findings suggested that MOF-encapsulated OPAA (or related enzymes) may be suitable for large area and personnel decontamination.

4.3.8 MOF Supporting Bed Used Along with Molecularly Imprinted Polymer

A novel approach to synthesize molecularly imprinted polymer (MIP) nanoparticles using a MIL-101 support (a type of MOF) known as MIL@MIP had been reported. The nanoparticles were well dispersed within the MOF films, showed an octahedral shape and exceptional thermal stability, and exhibit high specific surface area (SSA) of 1579.43 m^2/g (Qian et al. 2016). The adsorption behaviour of MIL@MIP towards metolcarb in aqueous solution had been investigated. The synthesized MIL@MIP displayed decent transfer mass rates and a high selective adsorption compatibility for metolcarb. Based on the results obtained, a quartz crystal microbalance (QCM) sensor based on MIL@MIP was subsequently assembled and inspected for the sensitive detection of metolcarb. Under optimum conditions, the detection limit of the arrangement evaluated in pear juice was found to be 0.0689 mg/L within a linear range of 0.1–0.9 mg/L. MIL@MIP–QCM system incorporates the advantages of MIL-101 and molecularly imprinted technology (MIT), therefore accomplishing high detection sensitivity and selectivity. The spectrum of pesticide sensing application of various types of MOF is briefly demonstrated in Table 4.1.

Table 4.1 A summary of the performance of MOF-based pesticide sensing platforms

S. no.	Methodology	Matrix	Detection range	Limit of detection	References
1	Chromatography (HPLC)	MSPE extracted magnetic MOF-5 composites	0.3–500 μg/L	0.04–0.11 μg/L	Ma et al. (2018)
2	Gas chromatography	TMU4/PES	0.015–50 μg/L	5–8 ng/mL	Bashtani et al. (2018)
3	Gas chromatography-MS	MOF $[(La_{0.9}Sm_{0.1})_2\ (DPA)_3\ (H_2O)]$	50–1000 μg/kg (procymidone) 200–1000 μg/kg (all other)	16–67 μg/kg (procymidone); 50–200 μg/kg (all others)	Barreto et al. (2010)
4	Chromatography (solid-phase sorption-based extraction techniques)	Magnetic porous carbon derived from bimetallic MOF	2–500 ng/L	0.39–0.70 ng/L	Liu et al. (2017)
5	Gas chromatography—uECD	A high SA (NPC) has been successfully synthesized by using the metal–organic framework ZIF-90 [ZIF-90-NPC]	0.3–50 ng/g	0.1–0.5 ng/g	Zhang et al. (2014)
6	Magnetic solid-phase extraction with HPLC-DAD	Fe_3O_4 @SiO_2/MIL-101 microspheres	5–200 μg/L for flusilazole and fipronil; 2–200 μg/L for chlorfenapyr and fenpyroximate	LOD—0.3–1.5 μg/L; LOQ—1–5 μg/L	Ma et al. (2016)
7	Chromatography (magnetic solid-phase extraction)	Active magnetic metal–organic framework (MOF) hybrid material was synthesized in the presence of magnetite (Fe_3O_4) particles—MIL-101 (Fe) [Fe_3O_4/MIL-101 nanocomposite]	1–100 ng/mL	0.21–0.28 ng/mL	Zhang et al. (2014)
8	Adsorption	Magnetic MOF Cu-based MOF using Fe_4O_3 GO beta cyclodextrin nanocomposite as magnetic core	10–100 mg/L	–	Liu et al. (2017)

(continued)

Table 4.1 (continued)

S. no.	Methodology	Matrix	Detection range	Limit of detection	References
9	Adsorption	Zn-btc	10–1000 µg/L	LOD—0.20–1.60 µg/L and LOQ—0.66–5.28 µg/L	Wang et al. (2017)
10	Adsorption	UiO67/GO	Maximum adsorption capacity ~2.855 mmol	–	Yang et al. (2017)
11	Adsorption	Cu-BTC@cotton composite	82 mg g^{-1}	–	Abdelhameed et al. (2016)
12	Optical fluorescence	ZnPO-MOF 5	1 µg/L to 10 mg/kg	0.456 nM	Xu et al. (2018)
13	Optical luminescence	LMOF 271 $[Zn_4(adc)_4(tppe)]$	–	22 ppb	Rudd et al. (2018)
14	Optical photoluminescnce	$[Cd_{2.5}(PDA)(tz)_3]$	–	16 ppb	Singha et al. (2017)
15	Optical florescence	Entangled L MOF $[Zn_2(bpdc)_2(BPyTPE)]$	0.94–16.92 ppm	0.13 ppm	Tao et al. (2017)
16	Optical photo-electrochemical detection	NH_2—MIL—125(Ti)/TiO_2@GCE	0.2–25 µmol/L	0.01 µmol/L	Jin et al. (2015)
17	luminescence/chemosensing	NMOF1	1–500 ppb	1 ppb	Kumar et al. (2014)
18	Electrochemical detection	NF/Ache/NF-Fe_2O_3@C/CPE		3.2×10^{-15} gm/mL	Wei et al. (2018)
19	Electrochemical immunosensing	Anti-atrazine antibodies/$Cu_3(BTC)_2$@SiO_2/BDC-PANI	0.01 nM^{-1} µM	0.01 nM	Bhardwaj et al. (2015)

(continued)

Table 4.1 (continued)

S. no.	Methodology	Matrix	Detection range	Limit of detection	References
20	Electrochemical sensing	Metal–organic framework based on 2,20,4,40-biphenyltetracarboxylic acid with a uninodal five connected hexagonal bnn was synthesized (MOF/GCE)	–	0.006 μg/mL	Wen et al. (2010)
21	SERS	MOF embedded AuNP. AuNP/MOF 199; AuNP/uio66; AuNP/uio 67	–	0.2 μM; 0.009 μM; 0.02 μM	Cao et al. (2017)
22	Hydrolytic degradation	OPAA@ PCN b128y	12 wt% loading capacity	–	Li et al. (2016)
23	Molecularly imprinted technology (MIT)	MIL Np@MIP-101/quartz crystal electrode	0.1–0.9 mg/L	0.0689 mg/L	Qian et al. (2016)

Abbreviations (*TMU4/PES*) Zn-based MOF/PES nanocomposite; *PES* polyether sulphone; *DPA* diphenyl amine; *NPC* nanoporous carbon; POM: polyoxometalate; *BTC*: benzenetricarboxylate; $D\text{-}H_2cam$ = D-camphoric acid; bimb = 4,4′-bis(1-imidazolyl) biphenyl; *BDC* benzenedicarboxylic acid

4.4 Conclusion

The chapter highlights MOF as a material for the pesticide sensing applications. Various approaches were used for the detection of the pesticides efficiently. As a result of their favourable structural and functional features (e.g. large surface area, tuneable porosity and utilitarian locales, adjustable luminescent qualities and complex associations with the guest species), MOF is a perfect platform for detection of pesticides. The sensing property of varieties of MOFs is analysed for their unique luminescent, optical, chromic, optical properties. The standards required for the pre-processing of a MOF design; by choosing appropriate natural linkers and metals focuses to tailor the structure. Likewise, the choice of a proper synthesis methodology is important to provide an ideal porosity and develop prevalent MOF with profoundly specific and proficient detecting capacities for a huge range of pesticides. Electrochemical detection of pesticides through MOFs is a promising field with various compound functionalities, and metallic particles assume a predominant part in deciding the affectability furthermore, selectivity of the sensor. Considering all parameters and essential difficulties related to MOF-based pesticide-detecting approaches incorporates the precariousness of MOFs (fluid, warm, dampness, light and mechanical), dispersion rates of analyte particles inside the system, rate of PL quenching and different concoction impedances. These constraints can be reduced or dispensed with distinctive propelled arrangements, for example, the joining of system catenation, anionic linkers, expansion of higher valency metal locales, stability analysis, enhancing conductivity inside the MOF structure, and fitting the porosity and functionalities of the MOFs. An incorporated approach will give balanced and precise MOF-based sensors that are field-deployable, financially savvy, versatile, delicate and quick in nature. Such advancements will help in the progression of MOF-based advances in the field of contamination control.

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Chapter 5
Recent Advances in Plant Pathogen Control by Nanocides

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Abstract Nanotechnology is a transformative technology and has the great potential to play an important role in world food production and its safety. The engineered nanomaterials possess novel properties due to their size, shape and morphology. These novel properties increase their ability to interact with living organisms. Recently, the use of nanoparticles in agriculture is exponentially increased in the form of nanopesticides, nanofertilizers and nanosensors. The main advantages of the nanoparticles over the conventional formulations, that are required in lesser quantity, which ultimately may reduce the losses in term of money and protect the environment. In this chapter, we have discussed the current use of nanoparticles and formulations for controlling the plant pathogens. The use of nanoparticles has the potential to enhance the suppression of crop diseases and subsequently enhance the sustainability in agriculture. We have also discussed the probable mechanism through which these nanoparticles act as nanocides. Last, we offer comments on the future aspects of these applications.

Keywords Antimicrobial activity · Plant pathogen · Metal nanoparticles · Nanocarriers · Toxicity mechanism

5.1 Introduction

Agriculture is the pillar of most developing countries like India and is one of the largest contributors towards their gross domestic product (GDP). Currently, agriculture faces major challenges like climate change, reduction of agricultural land, and increasing population and food demands. Antimicrobial resistance is another

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important factor that hampers the activity of existing fungicides and pesticides. Microbes not only destroy valuable crops but also cause economic losses. It has been estimated that plant diseases accounted for a 20–40% yield loss around the globe (Abd-Elsalam and Alghuthaymi 2015). Out of these, phytopathogenic fungi cause a loss of approximately $45 billion each year (Abd-Elsalam and Alghuthaymi 2015). These losses are huge when we consider an increasing world population to feed. Since every individual is directly or indirectly influenced by the agriculture sector, it is essential that these challenges faced by agriculture should be minimized.

Pesticides have been used to control insects, weeds, fungi and bacteria that infest the crops and have contributed significantly to crop production. Pathogen control efforts through fungicide applications exceed 600 million US dollars per year (González-Fernández et al. 2010). As a result, 25% of food crops worldwide are contaminated with toxins (Patel et al. 2014). Thus, over the course of time, there has been an increasing evidence of the hazards and disadvantages of these chemicals. The critical issues of pesticides includes the development of pesticide resistance, pest resurgence, environmental pollution, pertinacity of residue in food and soil, and damage to human health. These effects have now become more apparent than ever and have been studied extensively. The major disadvantages of fungicides/bactericides include the non-target toxicity to mammals (including humans) and microorganisms. Even though pesticides have specific target organisms, they may cause undesired toxic effects in non-target organisms also (Milenkovski et al. 2010; Johnsen et al. 2001; Kinney et al. 2005; Petersen et al. 2004).

Environmental impact of pesticides cannot be unseen either. Pesticides cause contamination of soil, water and vegetation. Apart from killing insects or weeds, pesticides can have a toxic effect on the host of other organisms like birds, fishes, beneficial microbes and desired crops (Aktar et al. 2009). Many studies suggest that the formation of biofilms could be the direct cause of antimicrobial resistance in various bacteria (Beyth et al. 2015). Biofilms are structured multicellular communities embedded in a self-produced extracellular matrix that acts as a barrier to antibiotic diffusion (Balcázar et al. 2015). Due to the presence of biofilms, bacterial cells are 10–1000 times less susceptible to specific antimicrobial compound when compared to their planktonic counterparts (Gilbert et al. 2002). The reduced susceptibility may be caused due to various factors, like, a poor antibiotic penetration into the polysaccharide matrix, the arbitrary presence of cells showing a resistant phenotype and the presence of either non-growing cells or cells that triggered stress responses under unfavourable chemical conditions within the biofilm matrix (Stewart and Costerton 2001).

Within the past half of the century, the evolution of a number of innovative technologies has revolutionized the biomedical sciences. Most notable among them is nanotechnology, covering broad interdisciplinary area of research and development. The word “nano” is used to indicate one billionth of a metre or 10^{-9} m. The concept of nanotechnology was given by Physicist Professor R. P. Feynman in his lecture ‘There’s plenty of room at the Bottom’ at California Institute of Technology in 1959 (Rai et al. 2009). During the last two decades, development in nanotechnology has opened the whole universe of new possibilities for biomedicine, agriculture and industry (Luksiene 2017).

Nanotechnology has potentional to revolutionize the agriculture sector with the tools like, delivery of fertilizers, nanoherbicides, insect pest management, nanofungicides and nanosensors. The aim of the development of nanomaterials is to increase the efficiency and sustainability of crops and to minimize the environmental consequences of the existing conventional products. In this chapter, we have summarized the use of nanoparticles and nanoformulations for fungal phytopathogen control.

5.2 Nanomaterials Against the Fungi

5.2.1 *Engineered Nanoparticles*

As a role, the properties of different materials drastically change as their size approaches the nanoscale. As the material becomes smaller, the percentage of atoms at the surface increases relative to the total number of atoms of the bulk material. At nanoscale, the surface-to-volume ratio of any material becomes larger and their electronic energy states become discrete, leading to unique electronic, optical, magnetic and mechanical properties of nanomaterials. Since the size of nanoparticles is similar to that of most biological molecules and structures, their application in biomedicine is unlimited (Rai et al. 2011). The metallic nanoparticles are most promising (Foster et al. 2011). The most important advantage of them is high stability under high temperatures and status of generally regarded as safe for human beings and animals (Li et al. 2009; Xie et al. 2011).

Several studies and experiments have been conducted to study the antimicrobial effect of nanoparticles on a variety of agricultural phytopathogens. These engineered nanoparticles range from metal nanoparticles like silver, zinc oxide, copper, platinum, titanium oxide and magnesium oxide to polymeric nanoparticles like chitosan and many more. This gives an insight into the wide scope of nanoparticles and their application and effect on pathogens. Some of these nanoparticles and their antimicrobial effects have been discussed below and summarized in Table 5.1.

5.2.1.1 Silver NPs

Silver (food additive, E 174) has been known from ancient times for its antimicrobial properties. As early as 1000 B.C., silver was used to make water potable (Castellano et al. 2007). In the 1940s, when penicillin was introduced in practice, the use of silver was minimized. Scientific society remembered it after 1960s, when experimental data confirmed high antimicrobial efficiency of silver nitrate and silver sulphadazine. Recently, silver nanoparticles have been used to treat wounds and infections (Rai et al. 2009). It has been studied that silver is effective against more

Table 5.1 Different nanoparticles and their antimicrobial effects

S. No.	Nanoparticles	Size	Fungi/Bacteria	Results	References
1.	Silver	10–20 nm	*Bipolaris sorokiniana* (common root rot and spot blotch of Barley)	Biosynthesized silver nanoparticles completely inhibited the conidial germination at all tested concentrations	Mishra et al. (2014)
		30–90 nm	*Colletotrichum coccodes* (Anthracnose on tomato and black dot disease of potato), *Monilinia* sp. (Brown rot) and *Pyricularia* sp. (Blast)	Synthesized nanoparticles by cow milk in concentration 2 mM significantly inhibit the growth of studied phytopathogens by 87.1, 86.5 and 83.5%, respectively	Lee et al. (2013)
		7–25 nm	Eighteen fungal species	Most fungi were inhibited at a 100-ppm concentration of silver nanoparticles	Kim et al. (2012)
		10–32 nm	*Macrophomina phaseolina* (Charcoal rot), *Alternaria alternate* (Leaf spot), *Fusarium oxysporum* (Fusarium wilt)	Highest inhibition rate observed at 400 μg/ml nanoparticle concentration for *M. phaseolina* and the least inhibition was observed at 50 μg/ml for *F. oxysporum*	Bahrami-Teimoori et al. (2017)
		–	*Rhizoctonia solani AG4* (damping-off), *M. phaseolina* (Charcoal rot), *Sclerotinia sclerotiorum* (crown rot and blossom blight) and *Pythium aphanidermatum* (Blight)	Concentrations more than 6 ppm resulted in complete inhibition of *S. sclerotiorum.* In *R. solani* all concentrations resulted in growth inhibition of 90% or above. For *P. aphanidermatum* and *M. phaseolina* complete growth inhibition was observed at all concentrations	Mahdizadeh et al. (2015)
		25 nm	*Colletotrichum* sp. (powdery mildews of cucumber and pumpkin)	At a concentration of 50 and 100 ppm silver nanoparticles inhibited the powdery mildew growth. When applied 3–4 weeks before the outbreaks, the nanoparticles were able to inhibit powdery mildew even at concentration of 50 ppm	Lamsal et al. (2011a)
		7–90 nm	*Alternaria zinniae* (leaf spot disease)	Green synthesized silver nanoparticles proved most effective with 73.9% inhibition of mycelial growth at all the tested concentrations	Negi (2016)
		31 ± 7 nm	*Phytophthora infestans*, *Alternaria solani* (Blight)	Better protection from *Alternaria* had been shown by nanosilver (73.1%) as compared to *Phytophthora* (59.1%)	Zakharova et al. (2017)

(continued)

Table 5.1 (continued)

S. No.	Nanoparticles	Size	Fungi/Bacteria	Results	References
		16.14 nm	*Gloeophyllum abietinum*, *G. trabeum*, *Chaetomium globosum*, *Phanerochaete sordida* (wood rotting pathogens)	NPs synthesized by turnip leaf extract showed broad-spectrum antifungal activity	Narayanan and Park (2014)
		6–38 nm	*Fusarium graminearum* (head blight of wheat), *F. oxysporum* (tomato wilt), *F. solani* (potato rot) and *Penicillium expansum* (apple rot)	The biologically synthesized AgNPs showed inhibitory effect in different concentrations (15 and 30 ppm)	Ali et al. (2015b)
		14.8 ± 1.2 nm	*A. solani* (tomato early blight)	At a concentration of 10 ppm maximum inhibition rates were induced in the mycelial growth in the three strains of *A. solani*	Abdel-Hafez et al. (2016)
		5–100 nm	*Aspergillus niger* (black mould of fruits)	NPs with the diameter of 27.4 and 26.8 nm, showed the maximum inhibition effect on the growth of the test fungus	Pandoli et al. (2016b)
		14.3 ± 3.6 nm	*A. niger* (black mould of fruits)	Homemade and commercial citrate-capped nanoparticles inhibit of fungal growth at a concentration of 2 mg/L	Pandoli et al. (2016a)
		15–30 nm	*Colletotrichum chlorophyte* (pathogen of various herbaceous plants)	In vitro and in vivo studies the nanoparticles were highly toxic to the fungi suggesting it as an alternative fungicide	Sukhwal et al. (2016)
		20–60 nm	*Phoma glomerata*, *Phoma herbarum*, *Fusarium semitectum*, *Trichoderma* sp., and *Candida albicans*	Ag-NPs significantly enhanced the antifungal activity of Fluconazole. Ag-NPs + Fluconazole showed the maximum inhibition effect against *C. albicans*, followed by *P. glomerata* and *Trichoderma* sp.	Gajbhiye et al. (2009)
		~17 nm	*R. solani*, *Neofusicoccum parvum*	At 40 ppm, 94.1 and 84% of *R. solani* and *N. parvum* growth were inhibited, respectively	Khatami et al. (2016b)
		22 nm	*Colletotrichum gloeosporioides* (papaya anthracnose)	Five times more synergistic effect of sodium deoxycholate-capped AgNPs against the endophyte was observed. The molecular marker studies have confirmed that AgNPs not shown any phytotoxicity	Shanmugam et al. (2015)
		1–22 nm	9 fungal species	Biosynthesized silver nanoparticles exhibited high antifungal activity against the tested fungi	Qian et al. (2013)

(continued)

Table 5.1 (continued)

S. No.	Nanoparticles	Size	Fungi/Bacteria	Results	References
		–	*Cercospora theae* (Bird's eye spot disease of tea)	Freshly prepared extracellular AgNps demonstrated a high inhibition rate of 59.42–79.76% against *C. theae*	Gnanamangai et al. (2017)
		5–30 nm	*Aspergillus flavus*	At a concentration of 150 ppm all five *A. flavus* isolates showed 100% inhibition	Al-Othman et al. (2014)
		7–21 nm	*F. oxysporum*	Biosynthesized AgNPs at 8 μg/ml showed strong antifungal activity against the tested fungi	Gopinath and Velusamy (2013)
		1–35 nm	*Agrobacterium rhizogenes*, *R. solani* and *A. tumefaciens*	Ag-NPs synthesized using *Descurainia sophia* showed maximum inhibition of *R. solani* (more than 86%) at 25 μg/ml	Khatami et al. (2016a)
		5–10 nm	*R. solani* (rice sheath blight disease)	The inhibition rate related to sclerotia germination at 5, 10, 25 and 50 ppm of Ag-NPs were 15, 26, 57 and 98%, respectively	Nejad et al. (2016)
		7–11 nm	*Dothiorella sarmentorum* (dieback)	More than 90% of the mycelia growth was inhibited by the Ag-NPs at concentrations of 40 μg/mL and above	Azizi et al. (2016)
		4–41 nm	*A. niger*	Epicatechin coated silver nanoparticles (ECAgNPs) with gentamicin showed remarkable antifungal activity against the fungus	Ikram et al. (2017), (2018)
		~12 nm	*Neofusicoccum parvum* (decline and dieback symptoms in grapevine)	The rate of inhibition at the concentration of 5, 10, 15 and 30 ppm of Ag-NPs were 41, 58, 68 and 81, respectively	Khatami et al. (2017)
		~21 nm	*Exserohilum turcicum* (northern corn leaf blight)	100% inhibition of conidia germination was achieved with 200 μg/ml AgNPs	Huang et al. (2018)
		22 nm	*Humicola insolens* (soft-rot fungus), *Mucor indicus*, *Fusarium dimerum*, *Trichoderma reesei*	At 50 μl, the prepared Ag-NPs were significantly active in inhibiting the tested fungal species	Vivek et al. (2011)
		4–8 nm	Six *Colletotrichum* species	Significant inhibition in mycelial growth was observed at concentration 100 ppm of silver nanoparticles	Lamsal et al. (2011b)
		5–50 nm	*Pseudomonas syringae*, *Burkholderia glumae* (bacterial panicle blight), *Xanthomonas oryzae* (Bacterial Blight of rice)	The zone of inhibition for *P. syringae*, *B. glumae* and *X. oryzae* were 8.9, 8.6 and 4.2 mm, respectively	Velmurugan et al. (2013)

(continued)

Table 5.1 (continued)

S. No.	Nanoparticles	Size	Fungi/Bacteria	Results	References
		15–18 nm and ~35 nm	*Botrytis cinerea*, *Penicillium expansum*, *Aspergillus niger*, *Alternaria* sp. and *Rhizopus* sp.	The antifungal activity of biosynthesized NPs using *Rhodotorula glutinis* (MIC—2 mg/L) was higher than that synthesized using *Cryptococcus laurentii* (MIC—4 mg/L). Moreover, biosynthesized NPs were more efficient than the chemically synthesized NPs	Fernández et al. (2016)
		10–15 nm	*Alternaria alternata*, *Sclerotinia sclerotiorum*, *Macrophomina phaseolina*, *Rhizoctonia solani*, *Botrytis cinerea* and *Curvularia lunata*	The growth of *A. alternata* and *M. phaseolina* was reduced considerably at 15 mg concentration, while others were not significantly reduced	Krishnaraj et al. (2012)
2.	Zinc Oxide	70 ± 15 nm	*Botrytis cinereal* (Botrytis bunch rot), *Penicillium expansum* (blue mould of apples)	Nanoparticles at concentrations greater than 3 mmol/l significantly decreased the growth of both the tested pathogens	He et al. (2011)
		(a) 25 nm (b) 40 nm	*R. stolonifer*, *A. flavus*, *A. nidulans* and *T. harzianum*	Results concluded that green ZnO nanoparticles exhibited better bactericidal and fungicidal effects than the chemically synthesized nanoparticles	Gunalan et al. (2012)
		20–30 ± 10 nm	*F. oxysporum*, *Sclerotium rolfsii* and *R. solani*	100 ppm ZnO showed mean inhibition of 63.39%	El-Argawy et al. (2017)
		Spherical: 27 ± 5 nm Hexagonal: 84 ± 2 nm	*A. flavus* and *A. niger*	Parthenium-mediated zinc oxide nanoparticles showed highest zone of inhibition at concentration 25 µg/ml of spherical-shaped nanoparticles against the tested pathogen	Rajiv et al. (2013)
		10 nm	*Peronospora tabacina* (blue mould in tobacco plant)	8 mg/L concentration of ZnO NP were successful in inhibiting leaf infection	Wagner et al. (2016)
		–	*R. solani*, *F. oxysporum*, *Sclerotium rolfsii*, *Colletotrichum truncatum*, *Alternaria alternate* and *Macrophomina phaseolina*	85.06, 71.75, 77.60, 88.87, 82.92 and 79.83% inhibition was observed for *R. solani*, *F.oxysporum*, *S rolfsii*, *C. truncatum*, *A. alternate* and *M. phaseolina* respectively at 100 ppm concentration of zinc nanoparticles	Dhoble and Kulkarni (2016)
		Different size	*Botrytis cinerea* (Botrytis bunch rot)	Both 1 and 5 mM nanoparticle concentrations lead to the inhibition of radial growth of the tested fungi. But, photoactivation of ZnO nanoparticles resulted in more pronounced antifungal effects	Kairyte et al. (2013)

(continued)

Table 5.1 (continued)

S. No.	Nanoparticles	Size	Fungi/Bacteria	Results	References
		30 nm	*Fusarium graminearum*, *Penicillium citrinum* and *Aspergillus flavus*	*P. citrinum* was completely inhibited by ZnO NP while *A. flavus* and *F. graminearum* were significantly reduced by ZnO NP	Savi et al. (2013)
		–	*A. niger and A. flavus*	The zone of inhibition diameter of pure zinc oxide against *A. niger* was found to be 11 mm for 100 μg/ml while that of aluminium doped zinc oxide against *A. flavus* was found to be 13 mm for 100 μg/ml	Srinivasan et al. (2015)
		<100 nm	*Fusarium graminearum*	The study proposed that the nanospecific effect of ZnO plays important role in antifungal effect. No toxic side effect of ZnO NP was reported in plants	Dimkpa et al. (2013)
		~57.72 nm	*Pseudomonas aeruginosa* and *Aspergillus flavus*	The green synthesized NPs at 25 μg/ml demonstrated the maximum zone of inhibition against *P. aeruginosa* and *A. flavus*	Jayaseelan et al. (2012)
		70 ± 15 nm	*F. oxysporum* (Fusarium wilt disease); *P. expansum* (grey and blue mould)	As ZnO NPs concentration was increased from 2 to 12 mg/L, the growth inhibition in *F. oxysporum* ranged from 19.3 to 77.5% and reduction rate of fungal growth in *P. expansum* ranged from 25.3 to 100%	Yehia and Ahmed (2013)
		15–20 nm	*F.oxysporum* (Panama disease of banana); *A. niger* (Black mould disease)	Zinc NPs strongly inhibited the radial growth of *A. niger* and *F. oxysporum* at all concentrations (50, 100, 250 and 500 ppm). The antifungal effect, i.e. radial growth reduction and ROS level increment was dose-dependent	Patra et al. (2012)
		20–25 nm	*A. flavus*; *A. fumigatus*	80 μg/mL concentration of ZnO nanoparticles reduced the fungal biomass by 75% after 7 days. Both 60 and 80 μg/mL showed excellent activity against tested fungi	Navale et al. (2015)
		2–28 nm	*Fusarium* sp.	At 0.1 M, ZnO NPs reduced the colony forming unit (cfu/ml) w.r.t. the control. Also, at the same concentration of 10–1 M, antifungal effects were observed	Sharma et al. (2010)

(continued)

Table 5.1 (continued)

S. No.	Nanoparticles	Size	Fungi/Bacteria	Results	References
3.	Silica	20–40 nm	*Fusarium oxysporum* and *Aspergillus niger* (maize pathogens)	The maize plants treated with nanosilica had higher expression of phenolic compounds, also resulted in down expression of stress-responsive enzymes	Suriyaprabha et al. (2013)
4.	Copper	20–50 nm	*Fusarium* sp. (tomato and dragon fruit plants)	93.98% inhibition of the fungal growth observed at 450 ppm Cu NPs concentration after a 9-day incubation period	Viet et al. (2016)
		–	*Micrococcus luteus*, *Pseudomonas aeruginosa*, *A. flavus* and *A. niger*	Antimicrobial activity is observed against all the tested microbes	Ramyadevi et al. (2012)
		~20 nm	*Alternaria alternate* (leaf spot) and *Botrytis cinerea* (grey mould)	Inhibition obtained at 15 mg/L concentration of copper nanoparticles	Ouda (2014)
		150 nm	*A. solani* and *F. oxysporum*	Copper–chitosan NPs at 0.12% concentration were the most effective disease control in tomato plants	Saharan et al. (2015)
		–	*Cercospora theae* (Bird's eye spot disease of tea)	Field studies have suggested that the use of bionanocopper at concentration of 1.5 ppm resulted in 66.1% disease prevention	Gnanamangai et al. (2017)
		11–55 nm	*Phytophthora infestans* (Late blight of tomato)	Three different copper NPs of similar sizes and shapes, Cu_2O, CuO and Cu/Cu_2O showed promising efficacy and produced no damages to the plants	Giannousi et al. (2013)
		5–10 nm	*Phoma destructive*, *Curvularia lunata*, *Alternaria alternata* and *F. oxysporum*	The CuNPs produced, exhibited good antifungal activity against the tested pathogenic fungi	Kanhed et al. (2014)
		~8 nm	*Alternaria alternata*, *Aspergillus flavus*, *Fusarium solani* and *Penicillium chrysogenum*	The fungal colonies reduced remarkably with increasing nanoparticle concentration. The MIC was observed <40 mg/L for *P. chrysogenum*, less than 60 mg/L for *F. solani*, *A. alternata* and less than 80 mg/L for *A. flavus*	Ghasemian et al. (2012)
		<50 nm	Soil-borne plant pathogenic *Pythium* sp.	The antimicrobial effect of CuO NP on Pythium was dose-dependent. Moreover, CuO NP were more effective than ZnO NP (<100 nm)	Zabrieski et al. (2015)
		3–30 nm	*Fusarium equiseti*, *F. oxysporum* and *F. culmorum*	Cu NPs showed the maximum antimicrobial activity against *F. equiseti*, followed by *F. oxysporum* and *F. culmorum* with 25, 20 and 19 mm diameter of inhibition, respectively	Bramhanwade et al. (2016)

(continued)

Table 5.1 (continued)

S. No.	Nanoparticles	Size	Fungi/Bacteria	Results	References
5.	Magnesium oxide	20–30 ± 10 nm	*F. oxysporum*, *Sclerotium rolfsii* and *R. solani*	100 ppm MgO showed 67.24% mean inhibition. Moreover, 100 ppm MgO NPs showed the most antifungal activity out of all nanoparticles in inhibiting *F. oxysporum*	El-Argawy et al. (2017)
		70 nm	*F. oxysporum*, *F. lycopersici*	2% concentration of MgO nanoparticles had the greatest effect on the tested pathogen	Parizi et al. (2014)
		~30 ± 10 nm	*Alternaria alternata*, *F. oxysporum*, *Rhizopus stolonifer* and *Mucor plumbeus*	MgO NPs at all concentrations produced maximum inhibition in the spore germination of all the tested fungi	Wani and Shah (2012)
6.	Chitosan	180.9 nm	*F. graminearum*	At 1000 ppm, chitosan NPs inhibited maximum mycelia growth	Kheiri et al. (2016)
		–	*C. albicans*, *A. niger* and *F. solani*	3 mg/mL of high and low molecular weight chitosan inhibits 90% of selected fungi species	Yien et al. (2012)
		–	*Alternaria solani* and *Fusarium oxysporum* (Tomato pathogens)	When used at 0.12% concentration the Cu-Chitosan NPs these nanoparticles resulted in the significant plant growth promotion, as well as antifungal abilities	Saharan et al. (2014)
		192.2 ± 2.5 nm	*A. alternata*, *M. phaseolina* and *R. solani*	A growth inhibition rate of 89.5, 63.0 and 60.1% was seen in *A. alternata*, *M. phaseolina* and *R. solani*, respectively	Saharan et al. (2013)
		~296.962	*Nigrospora sphaerica*, *Botryosphaeria dothidea*, *Nigrospora oryzae*, *Alternaria tenuissima*, *Gibberella zeae*, *Fusarium culmorum*	At 2 mg/mL oleoyl-chitosan NPs significantly decreased the radial growth of all the tested pathogens except for *G. zeae* and *F. culmorum*. With the concentration of NPs the inhibition of the pathogens was observed. At 2 mg/mL, the antifungal indexes for *N. sphaerica* and *B. dothidea* were 78.16 and 79.10%, respectively	Xing et al. (2016)

(continued)

Table 5.1 (continued)

S. No.	Nanoparticles	Size	Fungi/Bacteria	Results	References
7.	Titanium oxide	–	*F. solani*, *Venturia inaequalis*	The MICs of the Ag–h–TiO_2 NPs was 0.43 mg/plate for *F. solani* and 0.75 mg/plate for *V. inaequalis*. Moreover, the activity of the nanoparticles was enhanced when exposed to light	Boxi et al. (2016)
		20–30 ± 10 nm	*F. oxysporum*, *Sclerotium rolfsii*, *R. solani*	100 ppm concentration of TiO_2 nanoparticles showed 53.67, 100, and 78.89% inhibition in *F. oxysporum*, *S. rolfsii*, and *R. solani*, respectively	El-Argawy et al. (2017)
8.	Sulphur	~35 nm	*F. solani* (early blight and Fusarium wilt diseases of tomato), *Venturia inaequalis* (Apple scab disease)	Sulphur nanoparticles with size ~35 nm was very effective against tested fungi	Rao and Paria (2013)
		~20 nm (SNP1-using sodium polysulphide) ~50 nm (SNP-2 ammonium polysulphide)	*E. cichoracearum* (powdery mildew), *F. oxysporum* and sulphur-resistant fungus *A. niger*	It was observed that the activity of SNP-1 was better than SNP-2. At 2000 ppm, the hyphal structure of *F. oxysporum* were significantly deformed. While in *A. niger*, 2000 ppm of both nanoparticles distorted and collapsed the shafts of conidiophores significantly	Choudhury et al. (2011)
9.	Platinum	10–50 nm	*Colletotrichum acutatum* and *Cladosporium fulvum*	Pt NPs at 4 and 8 μg/well resulted in 15 mm and 18 mm zones of inhibition	Velmurugan et al. (2016)
10.	Gold	–	*Aspergillus niger*, *Fusarium oxysporum*	Significant and strong antifungal activity of different shaped and sized gold NPs was observed towards both fungal strains	Smitha and Gopchandran (2013)
11.	rGO nanosheets	5 μm	*A. niger*, *A. oryzae* and *F. oxysporum*	The half-maximal inhibitory concentration, values of the rGO nanosheets was 50 μg/ml against *F. oxysporum* and 100 μg/ml against *A. niger* and *A. oryzae*	Sawangphruk et al. (2012)
12.	β-D-glucan	60 nm	*Pythium aphanidermatum* (rhizome rot disease)	The prepared nanoparticle showed remarkable antifungal effects against the pathogen at 0.1% (w/v) concentration foliar application	Anusuya and Sathiyabama (2015)

(continued)

Table 5.1 (continued)

S. No.	Nanoparticles	Size	Fungi/Bacteria	Results	References
13.	Nitrogen-doped carbon nanohorn (NCNH)	3–4 nm	*R. solani*	At concentrations more than 100 μg/mL, the growth of the pathogen was decreased considerably	Dharni et al. (2016)
14.	MWCNT decorated with Ag, CuO and ZnO nanoparticles	–	*A. fumigatus*, *A. ochraceus*	Ag-CNTs, ZnO-CNTs and Ag-CNTs demonstrated maximum inhibition against *A. fumigatus*; while CNTs, CuO-CNTs and Ag-CNTs had the maximum inhibition effect against *A. ochraceus*	Fosso-Kankeu et al. (2016)
15.	Cobalt and Nickel nanoferrites ($CoFe_2O_4$ and $NiFe_2O_4$)	Average size of 25 nm	*F. oxysporum*, *Colletotrichum gloeosporioides*, and *Dematophora necatrix*	Shown antifungal activity against the all three-pathogen in vitro condition and reduced the in vivo incidence of Fusarium wilt in capsicum	Sharma et al. (2017)

than 650 pathogens. The antimicrobial effects of silver can be further been enhanced by engineering the size of silver to nanorange. Silver nanoparticles are now considered as an alternative to antibiotics and a viable option to work against multidrug-resistant pathogens (Franci et al. 2015; Rai et al. 2012; Salomoni et al. 2017). Various sizes of silver nanoparticles have shown antifungal and antibacterial effects against plant pathogens (Table 5.1). The size of the nanomaterial in all the cases is less than 100 nm. Vast majority of fungal species studies included and are not limited to *Botrytis cinerea*, *Penicillium expansum*, *Aspergillus niger*, *Alternaria* sp., *Rhizopus* sp., *Mucor indicus*, *Fusarium dimerum*, *Trichoderma reesei* and *Colletotrichum chlorophyte*. The nanoparticles are synthesized both chemically and biologically. Fernández et al. (2016) showed that biologically synthesized nanoparticles had a better antimicrobial effect as compared to chemically synthesized ones. Lamsal et al. (2011a) found in their study that silver nanoparticles of size ~25 nm were able to inhibit powdery mildew of cucumber and pumpkin even at a very low concentration of 50 ppm, when applied 3–4 weeks before the outbreak. While some studies focus only on silver nanoparticle-mediated antimicrobial effects, others combined silver nanoparticles with cholanoic acid, epicatechin, fluconazole, etc. to achieve enhanced antimicrobial effects.

5.2.1.2 Zinc Oxide Nanoparticles

Zinc oxide being food supplement is not only chemically stable but has a longer life than organic-based disinfectants (Li et al. 2009). It is important to note, that nano-sized ZnO particles exhibit some advantages in comparison with other nanoparticles due to their lower cost, white appearance and UV blocking properties (Dastjerdi and Montazer 2010). Moreover, antimicrobial properties of ZnO NP drastically increase under illumination with UV light due to induction of photocatalysis (Kairyte et al. 2013). But UV light has some disadvantage: due to relatively high energy, it destroys not just microbes, but other materials and surfaces as well. Recently, photoactivation of ZnO with visible light has proved to be more specific (Aponiene and Luksiene 2015). As a role, such photoactivation induces following production of reactive oxygen species (ROS), which ultimately damage cellular membrane and eventually kill bacteria. Eventually, this phenomenon can be successfully applied for development of alternative, environmentally friendly sunlight-activated nanobiofungicides. Zinc oxide nanoparticles exhibit strong antibacterial activities on broad-spectrum pathogenic bacteria and fungi. *B. cinerea*, *Rhizoctonia solani*, *Aspergillus flavus*, *A. niger*, *Fusarium oxysporum*, *Pseudomonas aeruginosa*, are some of the most common pathogens studied and mentioned in Table 5.1. Yehia and Ahmed (2013) observed 25–100% growth inhibition of *P. expansum* when concentration of ZnO NPs was varied from 2 to 12 mg/L. It was also seen that ZnO NPs had more inhibitory effects towards *P. expansum* than *F. oxysporum*. The antimicrobial effects of ZnO NPs in the studies were dose-dependent. Gunalan et al. (2012) concluded that the green ZnO nanoparticles exhibited better antimicrobial effects on *Rhizopus stolonifer*, *A. flavus*, *Aspergillus nidulans*, *Trichoderma harzianum* than chemically synthesized ZnO Nps. Experiments done by Kairyte et al. (2013) pointed towards the remarkable antimicrobial activity of photoactivated ZnO NPs against *B. cinerea* in the presence of visible light. Li et al. (2017) indicated that both ions and nanoparticles have significant inhibitory effects on *Sclerotinia homoeocarpa*, causing cool season turfgrasses disease, mycelial growth, while investigating ZnO nanoparticles and $ZnCl_2$ (Li et al. 2017). There is a lack of information about the damage of zinc for fungi; however, it was shown that zinc ions (from ZnO nanoparticles) inhibit multiple activities in the bacterial cell, such as glycolysis, transmembrane proton translocation and acid tolerance, while presence of only zinc ions (not ZnO nanoparticles) inhibit only bacteria proliferation and give only bacteriostatic effect (Seil and Webster 2012). The evidence of antimicrobial activity of these nanoparticles paves a way for their use as a potential weapon against plant pathogens in agriculture.

5.2.1.3 Copper Nanoparticles

Copper nanoparticles show multifunctional antibacterial activity, are cost-effective and can be considered ecologically safe (Holubnycha et al. 2017). In addition, it was found that, the copper nanoparticles have a significant antifungal activity against phytopathogenic fungi: *Curvularia lunata*, *Phoma destructiva*, *F. oxysporum* and *Alternaria alternata* at low concentrations, which helps to use it in the future as one of the important applied factors in the agricultural field (Kanhed et al. 2014). Viet et al. (2016) in his experiments on Fusarium fungus, obtained an exceptional inhibition rate of 93.98% after 9-day incubation period at 450 ppm concentration of Cu NPs. Like most nanoparticles, a concentration-dependent inhibition effect was observed. Copper–chitosan nanoparticles also displayed good results in pot experiments. 0.12% concentration of copper–chitosan nanoparticles effectively controlled early blight and Fusarium wilt disease in tomato plants. Biosynthesized copper nanoparticles using at 1.5 ppm showed better disease prevention (66.1%) as compared to synthetic copper nanoparticles (65.5%) (Gnanamangai et al. 2017). Most of the copper nanoparticles are within or less than 50 nm in size. In all experiments, the tested nanoparticles showed inhibitory effects.

5.2.1.4 Magnesium Oxide Nanoparticles

Among the other metal nanoparticles, MgO nanoparticles are easy to obtain and non-toxic. It possesses antibacterial effects for a range of microbes (Cai et al. 2018). Some of the studies on the effect of MgO nanoparticles on plant pathogens have been reviewed in Table 5.1.

5.2.1.5 Chitosan Nanoparticles

Chitosan nanoparticles are ideal for application due to their biodegradability and non-toxicity (Yien et al. 2012). Effect of copper chitosan nanoparticles (0.1%) by Saharan et al. (2013) showed growth inhibition rate of 89.5% for *A. alternata*. Oleoyl–chitosan nanoparticles have also shown considerable antimicrobial effects on *Nigrospora sphaerica*, *Botryosphaeria dothidea*, *Nigrospora oryzae* and *Alternaria tenuissima.* The nanoparticles exhibited the most considerable effects on *N. sphaerica* and *B. dothidea*, with antifungal indexes of 78.16 and 79.10%, respectively, at the 2 mg/mL concentration (Xing et al. 2016).

Similarly, effects of other nanomaterials like, Titanium oxide NPs, MWCNT decorated with Ag, CuO and ZnO nanoparticles, nitrogen-doped carbon nanohorn (NCNH), β-D-glucan, rGO nanosheets, gold nanoparticles, platinum NPs and sulphur NPs have also been studied for their antimicrobial effects on plant pathogens (Table 5.1). Due to the promising results, it can be said that the nanomaterials have a large potential to be used as fungicides or bactericides in agriculture applications.

5.2.2 Nanoemulsions

A nanoemulsion is a thermodynamically stable liquid dispersion of water and oil phase combined with a surfactant (Mason et al. 2006). Nanoemulsions appear transparent owing to the small droplets of the dispersed phase that are smaller than 25% of the visible light wavelength (Patel and Joshi 2012). Nanoemulsions are very fine dispersions and possess visual properties, viscoelasticity and differential drug loading which make them suitable for wide range of application such as drug delivery (Singh et al. 2017). The drug loading capacity of nanoemulsions makes them a novel tool to combat phytopathogenic microbes in agriculture. Antimicrobial nanoemulsions are highly stable oil-in-water emulsions composed of nanometer-sized, positively charged droplets that have broad-spectrum activity against enveloped viruses, fungi and bacteria (Myc et al. 2003; Pannu et al. 2009).

The extensive and long-term use of conventional fungicides has led to the appearance of fungicide-resistant pathogens (Brent and Hollomon 1998). This makes the pesticides less useful and only adds to the environmental problems if used further. Due to this reason, there has been an increasing focus on essential oil-based oil-in-water nanoemulsion formulations of fungicides due to their biocompatibility and eco-friendly nature.

Antimicrobial effect of several essential oil-based nanoemulsions has been explored so far. Eugenol, found in clove oil, possesses antimicrobial activity against a variety of plant pathogens (Wang et al. 2010; Morcia et al. 2012; Amiri et al. 2008). This property has been explored to formulate nanoemulsion with useful antimicrobial activity. Abd-Elsalam and Khokhlov (2015) formulated spherical eugene oil nanoemulsion (EON) of size 50–110 nm. Three different concentrations were used to evaluate the antifungal activity against *F. oxysporum* f. sp. *vasinfectum* (FOV).

EON completely inhibited the mycelial growth of all FOV isolates at 5% concentration. The antifungal effect of EON persisted even at all concentrations.

Antimicrobial studies of nanoemulsions on various microbes have provided promising results. One study on nanoemulsions comprising of 1% cetylpyridiniumchloride (CPC) with a mean diameter of 213.9 nm showed effective antimicrobial activity against *Acinetobacter baumannii*. It was observed that the nanoemulsion can effectively reduce the metabolic activities of *A. baumannii* in biofilms at high dilutions and showed consistent antimicrobial activity after exposure to extreme environmental conditions, proving its suitability for field utilization (Hwang et al. 2013).

Nanoemulsions have shown good antifungal activity and have been successful in inhibiting fungal growth in plants. Citronella essential oil and neem oil mixture-based nanoemulsions have shown a potent antifungal effect against *R. solani* and *Sclerotium rolfsii* (Ali et al. 2017). Olive oil-based nanoemulsion has shown antifungal effect on *Candida* and *Aspergillus* species by improving drug properties like solubility and permeability (Ansari et al. 2016).

Antifungal assay on Ag nanoemulsion found that the growth of *S. rolfsii* was strongly inhibited and in turn, the silver nanoemulsion promoted the growth of mung bean plants. Since toxic effects of silver nanoemulsion were observed at higher concentrations in the same study, thus, before recommending the use of emulsion in agricultural fields, the toxic levels should be tested, and an optimum concentration should be advised (Patel et al. 2014).

5.2.3 Nanocomposites

Nanocomposites are solids containing two (or more) nanometer size "regions" which differ in composition and/or structure (Roy et al. 1986). These nanomaterials are composites in which at least one of the phases exists in nanometer range. Nanocomposites are high-performance materials exhibiting property of unique designs and combination with many possibilities. Due to their prominent potential, these materials are useful in fields of packaging to biomedical applications. This is evident by the ever-growing industry with an average annual growth rate of 25% (Camargo et al. 2009). With the emergence of nanotechnology, various studies have utilized the use of nanocomposites for its antimicrobial activities. In this section, some of the nanocomposite formulations and their experimental results have been discussed which include their antimicrobial effect on various fungi and bacteria.

Silica–silver nano-sized composition has been studied for its effective control of plant diseases caused by fungi and bacteria. The composition had a uniform size of 1to 5 nm. At a concentration of 100 ppm, all the bacteria and fungi were completely inhibited. When tested against the powdery mildews of pumpkins, 0.3 ppm concentration of the nanocomposition effectively controlled the disease and completely disappeared after 3 days of spraying the leaves with the formula. Hence, the product successfully controlled plant pathogens (Park et al. 2006).

Nanocomposite using selenium and arabinogalactan was synthesized and a comparative study was done on the antimicrobial effect of pure arabinogalactan, selenium dioxide and selenium-arabinogalactan nanocomposite (Papkina et al. 2015). The nanocomposite of arabinogalactan and selenium (with 1.23% selenium content) synthesized was a water-soluble orange-red coloured powder. The shape of the prepared nanocomposite was almost spherical, and their size was in the range of 50–80 nm with average size 67 nm. The bactericidal effect of selenium nanocomposite was the most pronounced as compared to pure and selenium dioxide. Adding the selenium nanocomposite to the physiological saline with a culture of bacteria caused the strongest suppression of growth of *Clavibacter michiganensis* cells. The study revealed a dramatic change in peroxidase activity and plant growth inhibition induced by treatment with selenium dioxide but the negative effect of selenium dioxide on potatoes makes this compound unacceptable for *C. michiganensis* elimination from plants. The nanocomposite also possesses a pronounced bactericidal effect. Moreover, the nanocomposite does not exert negative effects on plants (Papkina et al. 2015).

Multifunctional Fe_3O_4/ZnO/AgBr nanocomposites have also shown promising antimicrobial activity towards plant pathogens (*Fusarium graminearum*). Microwave-assisted method was used to prepare the nanocomposites and SEM, TEM, EDX, XRD and VSM techniques were used to characterize the prepared nanocomposites. Out of all the prepared samples, the Fe_3O_4/ZnO/AgBr (1:8) nanocomposite demonstrated the best antifungal activity towards the tested pathogen. The prepared nanocomposite inhibited *F. oxysporum* in 60 min, which is lesser inhibition time compared to *F. graminearum* (120 min). The rate of inactivation was directly dependent on the concentration of nanocomposite. These results suggested that Fe_3O_4/ZnO/AgBr nanocomposites can be effectively used as fungicides in agriculture and wastewater treatment. The best advantage being the recycling process in which the nanocomposite can be extracted by the means of externally applied magnetic field (Hoseinzadeh et al. 2016).

Bio-nanocomposites using chitosan nanoparticles (CS) and pepper tree (*Schinus molle*) essential oil with size range 200–600 nm have also been synthesized by nanoprecipitation method and their effect on the viability of *Aspergillus parasiticus* spores has been studied. Results showed that viability of fungal spores was reduced in all treatments but was concentration-dependent, i.e. smaller number of viable spores were observed in higher concentrations of bionanocomposite. A decrease of 40–50% in *A. parasiticus* was seen at the highest concentration of formulated bionanocomposite (Luque-Alcaraz et al. 2016).

Recent report has shown the phytotoxicity of silver functionalized titanate nanotubes (AgTNTs) to *B. cinerea*. The thickness of AgTNTs was about 11 nm with four layers, and the length was up to 300 nm. In 20 min, the nanocomposite caused rapid inhibition of the *B. cinerea*. In the initial 5 min, even though some intact conidia remained, the nanocomposite started to destroy some conidia by the photoactive silver-titanate nanotube effect under visible light, further affecting other conidia gradually. After 5 min, the cells started to lose density which was seen from the field emission scanning electron microscope (FESEM) imaging showing swollen vacuoles. After 45 min, it was observed that all the vacuoles were empty and silver-titanate bundles were present. Silver-titanate deposits caused an irreversibly inactivated the conidia of *B. cinerea*. Further, silver-titanate deposits were observed inside the inner layer of the cell wall and on the external layer of the cell wall which was verified by the TEM images (Rodríguez-González et al. 2016).

5.2.4 Nanogels

Nanogels are three-dimensional hydrogel materials in the nanoscale size range formed by crosslinked swellable polymer networks with a high capacity to hold water, without actually dissolving into the aqueous medium. Nanogels can be composed of a variety of naturally occurring polymers, synthetic polymers or a combination thereof (Soni et al. 2016). Nanogels are insoluble in water and consequently less prone to shrinking or swelling with changing humidity (Bhagat et al. 2013). Nanogels have shown a slow degradation and controlled release of active ingredient (Chhipa 2017). Nanogels can be the next generation biopesticides. To prove their effectiveness against microbes, experiments have shown promising results. Copper (II)-chitosan nanogels have exhibited strong synergistic effect against *F. graminearum* compared to chitosan solution and chitosan nanodispersion. The nanogel was obtained by mixing copper acetate solution of different concentrations with chitosan nanogel suspension in a 50 mM ammonium acetate/ acetic acid solution overnight at room temperature. The formation of Cu-chitosan nanogel depended on pH and the release of copper could be triggered by the decrease in pH (protonation of chitosan amino groups). The MIC for inhibition of *F. graminearum* of copper (II), chitosan solution and chitosan nanodispersions were determined as 250 μg/mL, 10 mg/mL and 17.5 mg/mL, respectively. With effective results, nanocolloidal chitosan particles are a promising, biocompatible pesticide (Kheiri et al. 2016).

A patented technology based on copper-loaded silica-based nanogel (CuSiNP/ NG) used to treat citrus canker, inhibit the growth of mould and mildew and add nutrients to soil. The formulation not only provide better antibacterial activity than tradition copper-based compounds but also provides sustained and optimal Cu ion release for long-term disease protection, better adherence to plant surfaces and structural surfaces due to gel-based nanostructure of CuSiNG. Thus, the silica-based nanoformulation releases copper in non-toxic quantities to the environment and the silica matrix provides an environmentally safe host material with a flexible design that is optimized to provide specific antifungal and antibacterial remediation using infrequent applications (Santra 2014).

When the effect of *O*-carboxymethyl chitosan (CMCh) on *A. flavus* was studied, it showed an inhibition zone diameter of 18 mm. Whereas CMCh/PVA nanogel (1:2) and CMCh/PVAA nanogel (1:1) exhibited a higher effective zone of inhibition of 35 and 30 mm, respectively. This finding pointed towards the fact that the antimicrobial activity of the prepared nanogels increases with the increase of PVA content (Farag and Mohamed 2012).

Plant essential oils have been known to possess antimicrobial properties and are considered as natural food preservatives and a good alternative to synthetic fungicides. Experiments have investigated an enhanced antimicrobial activity of plant oils by encapsulating them into nanogels. It has been seen that this improved the performance of plant oils as antimicrobial agents. *Mentha piperita* essential oil-based chitosan–cinnamic acid nanogels have been studied to enhance the antimicrobial activity and stability of the oils against *A. flavus*. The results presented that the encapsulation of *M. piperita* essential oils improved its antifungal activity remarkably. Without encapsulation, the oils are volatile and unstable due to environmental factors. The minimum inhibitory concentration (MIC) of encapsulated oils was 500 ppm while that of without encapsulation was 2100 ppm. Also, under non-sealed conditions, the MIC of encapsulated oil was 800 ppm while the free oils did not cause complete inhibition even at 3000 ppm. These results revealed that CS–Ci nanogels are a promising tool as a carrier for essential oils for the enhancement of their antimicrobial activity (Beyki et al. 2014).

Thyme essential oils have shown significant antifungal activity when encapsulated in chitosan and benzoic acid nanogel (CS–BA). The MIC of free thyme essential oil and encapsulated oil in CS–BA nanogel on *A. flavus* was compared under sealed and non-sealed conditions. Under sealed conditions, the MIC of encapsulated oil and free oil was 300 and 400 mg/l respectively. Under non-sealed condition, the encapsulated oil could inhibit the fungal growth at an elevated concentration of 500 mg/l while the free oil could not completely inhibit the growth even at a concentration of 1000 mg/l. In vivo study revealed antifungal activity of encapsulated oil at concentration >700 mg/l. It was seen that the CS–BA nanogel encapsulation not only increased the antifungal activity of the oil but also significantly increased its half-life (Khalili et al. 2015).

A study also pointed out the excellent antifungal activity of Chitosan–caffeic acid nanogel (CS–CA) encapsulated cumin (*Cuminum cyminum*) essential oils against *A. flavus*. Under sealed conditions, the MIC of free cumin essential oils was 650 ppm and that of encapsulated oil was 350 ppm. The encapsulated oil also performed better when tested under non-sealed conditions, whereas the free oil failed to completely inhibit fungal growth within the test range of 1000 ppm (Zhaveh et al. 2015).

5.2.5 Nanoparticles as Active Compound Carriers

Conventional pesticide application poses limitation like loss by leaching, evaporation and degradation which not only cause environmental pollution but also economic losses. This calls for a more efficient technology. Improved specificity, ease of handling, safety and lesser ecological disadvantages are some of the advantages of smart delivery systems made using biodegradable polymers. Adding to these are the nanoscale delivery systems which have advantages like huge surface area to volume ratio which enhance the bioavailability and thus offer lower application rates. Nanomaterials have been incorporated with pesticides for a better carrier and delivery systems in plants.

Various types of polysaccharide materials are chitosan, polyethylene glycol, starch, cellulose and polyester substances. Juglone-loaded poly-(D,L-lactic-co-glycolic acid) PLGA nanoparticle system has been synthesized and compared with free juglone for their antifungal properties against *A. flavus*, *Fusarium* spp. and *Candida albicans*. Antifungal studies indicated that juglone-encapsulated nanoparticles were more effective than free juglone. The lowest minimum inhibition concentration (MIC) value for the juglone-encapsulated PLGA nanoparticles and free juglone against *C. albicans* were 31.25 and 62.5 μg/mL, respectively. Results concluded that the juglone-loaded PLGA nanoparticles were more effective than free juglone in the inhibition of fungal growth (Arasoglu et al. 2016).

Chitosan nanoparticles loaded with *Satureja khuzestanica* essential oil when tested on *R. stolonifer* in tomato showed strong antimicrobial and antioxidant activity. The effect of encapsulated oil (chitosan and oil in 1:1 ratio) was studied and recorded for 9 days. The rotting of tomatoes decreased, and growth of fungi was also controlled (Amiri and Morakabati 2017). A study on the effect of chitosan-poly(lacide) copolymer (CPLA) nanoparticles loaded with the fungicide Pyraclostrobin on *Colletotrichum gossypii Southw* was conducted. The study compared the antifungal activity of 25% pyraclostrobin emulsifiable concentrate (EC) and pyraclostrobin-loaded CPLA nanoparticles. The results showed that the percentage inhibition by 25% pyraclostrobin EC on third, fifth and seventh days were 37.0–81.5%, 48.1–86.5% and 40.3–83.6% (for at different concentrations), respectively, compared to the percentage inhibition by pyraclostrobin-loaded CPLA nanoparticles on same days (11.1–81.5%, 42.3–84.6% and 52.2–85.1% on third, fifth and seventh day, respectively). Even though the results indicated a better percentage inhibition by 25% emulsifiable concentrate (EC) against *C. gossypii* from day 1 to 3, the antifungal activity of nanoparticles was better than that of the free fungicide. Also, the active compound (fungicide) was more stable in nanoparticles, the loaded nanoparticles revealed an initial burst, subsequent pH-controlled behaviour and the bioactivity results exhibited sustained release profile. Conclusively, the loaded nanoparticles had high loading and encapsulating efficiency, sustained release profile and environmental compatibility (Xu et al. 2014).

Chitosan nanoparticles (CSNP) crosslinked with sodium tripolyphosphate encapsulated with loaded *Zataria multiflora* essential oil (ZEO) increased the activity of the essential oil against fungus *B. cinerea*. A significant decrease in disease severity and incidence of Botrytis-inoculated strawberries during 7 days of storage at 4 °C followed by 2–3 more days at 20 °C was observed in the in vivo experiment at a 1500 ppm concentration of encapsulated oil. In vitro studies revealed that ZEO was unable to inhibit the growth of mycelia even at a concentration of 1500 ppm, whereas when ZEO was encapsulated by chitosan nanoparticles, the produced nanoencapsulation completely inhibited the fungal growth at a concentration of 1500 ppm (Mohammadi et al. 2015).

Another study on the antifungal effect of chitosan crosslinked with sodium tripolyphosphate (TPP) nanoparticles obtained by ionic gelation against plant pathogenic fungi *A. parasiticus* demonstrated the toxic nature of the synthesized nanoparticles to the tested fungi. It was further noticed that the antifungal effect increased as the particle size decreased. The inhibitory effects were also more pronounced than that of chitosan solution. Moreover, the effect on the spore germination was dependent on the TPP concentration (Cota-Arriola et al. 2013).

A co-delivery system using methoxypolyethyleneglycol-poly (lactide-co-glycolide) nanoparticles have been used for the encapsulation of two pesticides simultaneously, viz. validamycin and hexaconazole, and the efficacy of the co-delivery NPs against *Rhizoctonia cerealis* was also studied. The nanoparticles showcased a better antifungal activity compared to the traditional pesticide formulation. The noteworthy observation was the percentage of relative inhibition of the growth of the fungus increased with the time of exposure to nanoparticles and decreased with time of exposure to a commercial preparation (Zhang et al. 2016).

Controlled release nanoformulation of the fungicide carbendazim has been prepared using poly (ethylene glycols) (PEGs)-based functionalized amphiphilic copolymers and their effect on *R. solani* have been studied. It was seen that the release of a maximum amount of carbendazim from the formulations increased with increasing molecular weights of PEGs i.e., the release was dependent on the molecular weight of PEGs. The formulations showed excellent fungicidal activity against the tested fungi and the ED_{50} (effective dose for 50% inhibition) values vary from 0.40 to 0.74 mg/l (Koli et al. 2015).

Another PEG-based nanoformulation using Mancozeb (fungicide) has been synthesized and evaluated for its bio-efficacy against *Alternaria solani* and *S. rolfsii*. The formulation is eco-friendly and does not contain any surfactants or external additives. The ED_{50} values of the nanoformulation varied from 1.31 to 2.79 mg/l for *A. solani*, and 1.60 to 3.14 mg/l for *S. rolfsii* (Majumder et al. 2016).

Several studies have been done to study the effect of pesticides combined with metal nanoparticles on various microbes. It has been seen that the antimicrobial activity of pesticides was enhanced and was better than that shown by the pesticides alone. Silver nanoparticles with ketoconazole showed synergistic inhibitory activity against *A. flavus*, *A. niger*, *Aspergillus tamarii*, *A. versicolor*, *Macrophomina phaseolina* and *Penicillium* sp. better than Ag nanoparticles and ketoconazole alone. This kind of formulations can be used for enhancement of antifungal activity of other entity useful in food industries to control fungal contamination (Jogee et al. 2017). Another example includes the antifungal activity of silver nanoparticles when combined with fluconazole against the pathogens, *Fusarium semitectum*, *Phoma herbarum*, *Phoma glomerata*, *C. albicans* and *Trichoderma* sp. The nanoformulation produced maximum antifungal efficacy against *C. albicans* followed by *Trichoderma* sp. and *P. glomerata*, whereas for *F. semitectum* and *Phoma* *herbarum,* there was no enhancement in the antifungal efficacy by the use of silver nanoparticles + fluconazole (Gajbhiye et al. 2009).

Zinc oxide nanoparticles combined with thiram (fungicide) showed a dose-dependent activity against tested fungi *Phytophthora capsici*. Results showed 0.25 g/L zinc oxide nanoparticles with 0.01 g/L thiram could inhibit 90% of the fungal growth in a synergistic mode. The finding suggested the optimal usage of ZnO NPs degraded thiram residue to safety level efficiently (Xue et al. 2014).

5.3 Mechanism Behind the Various Nanocides

The synthesis of nanomaterial and their antimicrobial effect is well documented and widely studied. The mechanism, however, remains debated and thus requires more in-depth studies. To make optimal the use of nanoparticles in medicine and agro-food sector, and to assist the development of powerful, but not toxic antimicrobial derivatives, it is necessary to understand the mechanism of action of these nanoparticles against microorganisms. Moreover, it is crucial to know the mechanism of action as it will help to develop more efficient drugs. Studies have been conducted to learn more about the process of antimicrobial activities of nanomaterials. Recently, the antimicrobial activity of nanoparticles may be explained in several ways:

1. First, the nanoparticles can directly interact with the microbial cells, e.g. binding to the bacterial surface due to the electrostatic forces (Kon and Rai 2013). Microorganisms, including fungi and bacteria, have negative zeta potential (between −20 and −27 mV) (Chwalibog et al. 2010), while, for instance, ZnO nanoparticles have positive charge, with zeta potential +24 mV (Zhang et al. 2008). As a result, opposite charges between microorganisms and nanoparticles generate electrostatic forces, leading to a strong binding, which consequently damages cell membrane (Anitha et al. 2018). Jiang et al. (2009) propose different attachment mechanisms of metal oxide nanoparticles to bacteria. It includes Van der Waals forces, electrostatic forces, hydrophobic and dominating receptor–ligand interactions.
2. Second, NPs can produce secondary products (ROS) that cause cell destruction (Zhang et al. 2007). It is clear from experiments that both nanoparticles and ion species exhibit strong antimicrobial activity. But, the cellular and molecular mechanism of the microbicidal effect of nanomaterials has only been hypothesized and requires more insight. It is apparently the multiple pathways by which the nanomaterials cause cell destruction of microbes that make the clarification a difficult task (Slavin et al. 2017) (Fig. 5.1).

Several studies have been conducted on silver nanoparticles and their antifungal properties on various pathogens. The mechanism of how it inhibits the fungal growth, however, remains a topic of debate and only theories have been given

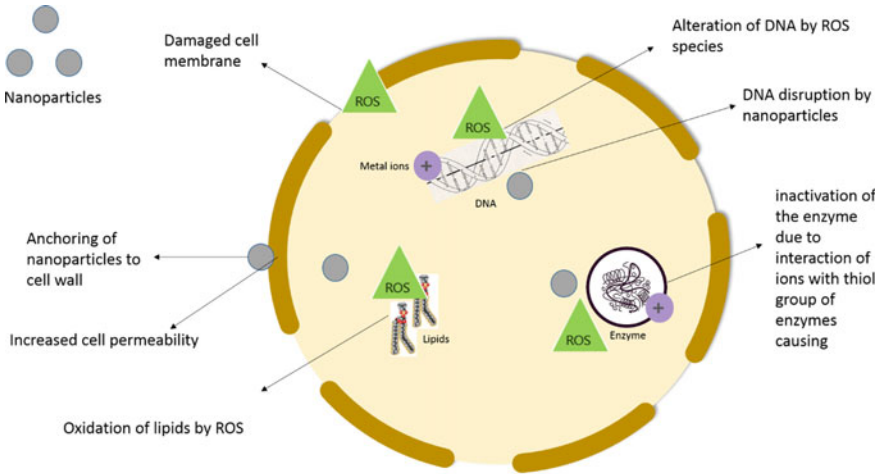

Fig. 5.1 Probable mechanism of nanoparticles causing antimicrobial effect

(Prabhu and Poulose 2012). Some studies suggest that silver nanoparticles anchor to the cell wall of the pathogen and eventually penetrate it, causing changes in the cell structure like the permeability of cell membrane which ultimately lead to death of the cell (Sondi and Salopek-Sondi 2004). It has also been hypothesized that silver ions can inactive many important enzymes by interacting with their thiol group (Matsumura et al. 2003). Ocsoy et al. suggested a similar theory where Ag^+ ions interact with the amino, carboxyl, thiol, phosphate and imidazole groups present in proteins and enzymes on bacterial membranes, causing a deformation in the cell membrane structure. This makes the membrane more vulnerable and, more and more Ag^+ ions penetrate into cells, deactivate critical enzymes, inhibiting the cell replication, and finally leading to the death of the cell (Ocsoy et al. 2013). Formation of free radicals by silver nanoparticles can be another reason for its antimicrobial activity as free radicals have the potential to disrupt the cell membrane of the microbe thereby making it porous and subsequently causing the death of cell (Danilczuk et al. 2006; Kim et al. 2007). Hatchett and White highlighted that silver being a soft acid and the possibility of it reacting with the soft bases, viz. sulphur and phosphorous present in DNA. This reaction of silver with the sulphur and phosphorous causes the DNA to lose its integrity, which consequently kills the cell (Hatchett and White 1996). Experiments conducted by Wani and Ahmad on the effect of gold nanoparticles on *Candida* showed gold nanoparticles interfere with the proton pump of the fungi. The study showed that the proton pump of the microbe was affected by the presence of nanoparticles. The ability to pump out protons to the external medium was reduced to 45% and 51% by 25 nm gold nanodiscs and 30 nm polyhedral gold nanoparticles, respectively (Wani and Ahmad 2013). Various nanoparticles such as, nitric oxide releasing nanoparticles, chitosan containing nanoparticles and meatal nanoparticles help in the prevention of development of resistance by combating the microbe through multiple mechanisms (Knetsch and Koole 2011).

Another mode of action of nanoparticles includes their ability to release reactive oxygen species (ROS). ROS is a term used for the molecules that have high positive redox potential. These species are produced by the reduction of oxygen molecules by nanoparticles. There are four types of ROS: singlet oxygen (O_2), hydroxyl radical (–OH), superoxide radical (O^{2-}), and hydrogen peroxide (H_2O_2) (Wang et al. 2017). ROS-induced oxidative stress is an important antibacterial mechanism of NPs. The main factor for the in vitro and in vivo cytotoxicity of nanoparticles is the generation of ROS and the affinity of ROS to associate with R–SH group. High levels of ROS are harmful to the eukaryotic cells. At lower levels, ROS governs several cellular functions and is thus desirable but when the levels increase above optimum levels, these ROS cause oxidative stress which in turn cause the alteration in lipid, proteins and DNA, finally causing cell death. (Slavin et al. 2017; Zhao and Nalwa 2007; Halliwell and Gutteridge 2015; Oberdörster et al. 2005).

Many studies have found that Gram-negative bacteria are less resistant to NP as compared to Gram-positive bacteria because of the presence of a layer of lipopolysaccharides, which carry a negative charge that has the affinity for the positive ions of the NPs, resulting in uptake of ions and thus causing cellular damage (Slavin et al. 2017).

Studies have suggested that the primary mechanism of cytotoxicity towards cell is the adsorption of nanomaterial on the cell membrane followed by its disintegration into the cell (Slavin et al. 2017). When nanoparticles are absorbed into the cell, it causes changes in the cell wall. The cell wall which is typically negatively charged depolarizes, and it becomes more permeable. When observed under a laser scanning confocal microscope, the bacterial cell wall is reported to become blurry due to the depolarization caused by nanoparticles (Mukha et al. 2013). Another study hypothesized a two-mode mechanism for the action of silver nanoparticles on the microbial cell. The first step involves the destruction of the cell wall by the nanoparticles followed by the penetration of nanoparticle into the cell. The second step involves the formation of ROS which inhibits the production of ATP and DNA replication, therefore leading to cell destruction. ROS plays a crucial role in the primary step since its production has been proved to hinder the cell's built-in antioxidant defence leading to consequent cell damage (Ramalingam et al. 2016). Silver nanoparticles have been studied widely for their antimicrobial effect. The experimental studies conducted on the fungi, *Aspergillus* showed that AgNPs inhibited the growth of *A. flavus* by affecting the cellular functions which caused deformation in fungal hyphae. AgNPs caused a reduction in spore number, malformation and hypertrophy, and these effects lead to the destruction of spores (Al-Othman et al. 2014). To understand the mechanism of the effects of nanoparticles on the pathogen, Ramalingam and co-workers proposed a possible mechanism for the toxicity of silver nanoparticles on the properties of *Escherichia coli* and *P.aeruginosa*. Intracellular ROS assay, live/dead fluorescence microscopic images and zeta potential analysis showed the production of ROS along with the interaction of Ag-NPs with the bacteria and the subsequent rupturing of the cell membrane which caused the cell death AFM images revealed that following the exposure to silver nanoparticles, the cell integrity was lost and cellular debris was found around the cell. It can be concluded from the zeta potential and DLS studies that the destabilization of membrane caused by ROS can be a reason for the neutralization of surface charge of the cell which subsequently leads to cell death. Due to the interactions with Ag-NPs, the physical attributes such as rigidity, adhesion and the roughness of the cell membrane changed. They pointed out the denaturation of the cell membrane protein, destruction of phospholipid groups and glycoside linkages of polysaccharides (Ramalingam et al. 2016).

Carbon nanotubes (CNTs) possess antifungal properties have also been reported. The antifungal effects are caused by the oxidative stress from the carbon-based compounds. The oxidative stress consequently causes the membrane damage in microbial cells (Dizaj et al. 2015). Not only that, it has also been proposed that carbon nanotubes cause the fungi to starve by absorbing the nutrients from the environment, thereby creating a nutrient-deprived environment (Fosso-Kankeu et al. 2016).

Espitia and colleagues reported that the deformation of the hyphal cell structure in fungi might be addressed to excessive accumulation of nucleic acids and carbohydrates, since ZnO NPs can affect cell physiology and trigger higher production of nucleic acids. Moreover, the increase in the production of nucleic acids can be considered as a stress response of fungal hyphae, and increase in production of carbohydrates may be the result of cell self-protection from action of ZnO NPs (Espitia et al. 2012). Wheat seeds can serve as suitable model for food system which is highly contaminated with micromycetes. Our previous work revealed that most of these microfungi belong to *Rhizopus* spp., *Aspergillus* spp., *Penicillium* spp., *Mucor* spp., *Fusarium* spp. and *Alternaria* spp. (Lukšienė et al. 2007). Results obtained indicate that the number of pathogenic and harmful micromycetes was significantly reduced (70%) after the treatment with photoactivated ZnO NPs, while NPs in the dark caused just $\sim$20% reduction of CFU compared to control.

The mechanism of antimicrobial effect of copper nanoparticles has also been hypothesized in various experiments. It has been observed that the bacteria were destroyed due to the copper nanoparticles interaction with the sulphhydryl (–SH) groups (Das et al. 2010; Schrand et al. 2010). The helical structure of DNA also gets disturbed by its interaction with the copper nanoparticles (Kim et al. 2000). It has been reported that the transmembrane electrochemical potential of the cell membrane of bacteria decreases due to its interaction with Cu nanoparticles, thereby destroying the cell membrane integrity (Deryabin et al. 2013). It has been assumed that possibly metal ions are released by metal nanoparticles. These metal ions form pits in the cell membrane by accumulating on the cell surface of the bacteria. This further causes leakage of cellular material from the inside of the cell. This leakage causes oxidative stress which finally leads to cell death (Deryabin et al. 2013; Ali et al. 2015a; Saleem et al. 2017).

Hypothesized mechanisms for the action of nanomaterials are not limited to nanoparticles alone. Nanoemulsion has shown excellent antimicrobial activity as well. Eugene oil nanoemulsion (EON) confirmed the inhibition of the tested fungi, *F. oxysporum* f. sp. *vasinfectum* (FOV). Abd-Elsalam and Khokholov also successfully tested the antimicrobial effects of eugene oil nanoemulsion on cottonseed (Abd-Elsalam and Khokhlov 2015). Eugenol, being a lipophilic compound, enters the fatty acid chains of the membrane lipid bilayers and finally alters the fluidity and permeability of the cell membranes (Braga et al. 2007; Gill and Holley 2006). These observations were further supported by staining of the eugenol-treated conidia of FOV.

The mechanism of antimicrobial effect of Cu-chitosan nanogel is not completely understood and hence is difficult to explain. However, studies have shown that chitosan induces leakage from lipid vesicles (Kong et al. 2010). Toxicity of copper nanoparticle can be associated to its potential to catalyse the production of hydroxyl radicals which can cause subsequently damage biomolecules in the cell, viz. lipids, proteins, DNA, etc. (Borkow and Gabbay 2005). So, it may be possible that small amounts of chitosan and copper can significantly disrupt the integrity of the membrane thereby enabling more copper to get inside the cell, leading to further cell damage (Brunel et al. 2013).

Mitra et al. studied the effects of zinc oxide nanoparticles embedded in mesoporous nanosilica ($ZnO@mSiO_2$) on *F. oxysporum* and *A. niger*. It was observed that the prepared nanomaterial had the ability to induce oxidative stress through the generation of ROS. Increased levels of superoxide dismutase (SOD), ascorbate peroxidase, etc. were a result of the increased oxidative stress due to ROS generation. Also, glutathione reductase (GR) involved in the prevention of damage caused by oxidative stress recorded an increased activity. Zn^{2+} ions released from $ZnO@mSiO_2$ played a role in the antimicrobial effect of the nanoparticles. Therefore, both ROS and Zn^{2+} ions contributed to the toxic effects of $ZnO@mSiO_2$ towards *A. niger* and *F. oxysporum* (Mitra et al. 2015).

With the help of SEM and Raman spectroscopy data, he and co-workers hypothesized that there may exist different mechanisms of action of ZnO NPs for two different fungi (*B. cinerea* and *P. expansum*). In case of *B. cinerea*, ZnO NPs inhibited the growth of the fungi by interfering with cell function and causing deformation in fungal hyphae, whereas in case of *P. expansum*, ZnO NPs led to a complete growth inhibition by inhibiting the development of conidiophores and conidia (He et al. 2011).

5.4 Impact on Environment and Human Health

It is estimated that worldwide consumption of NPs is likely to grow from 225,000 metric tonnes to nearly 585,000 metric tons for 2014–2019 years (BBC Research 2014). Moreover, NPs are estimated to be absorbed 12–20 times more than their bulk particles (Srivastav et al. 2016). Thus, rapid development of nanotechnology and wide application of nanoparticles in medicine, industry and agro-food sector has raised concerns about potential impact of nanoparticles on human health and environment. Let us look deeper in the living systems. For instance, zinc is necessary compound for plenty of cellular metabolic reactions and optimal functioning. Moreover, zinc is signalling ion in any cell signalling net. Moreover, it is present in 3000 human proteins where Zn interacts with N, O and S donors of the side chains of histidine, glutamate/aspartate or cysteine. ZnO interacts with H^+ and produces hydrated $Zn^{2+}(aq)$. It interacts with water and produce $Zn(OH)_{2.}$ The last can interact with hydrogen and produce phosphate ($HPO_4{}^{2-}$), sulphate ($SO_4{}^{2-}$) or chloride, which are normally present in every cell at millimolar concentration ($ZnCl_2$, $ZnSO_4$, etc.). Usually, the concentration of (free) not bound to protein zinc ions in the cellular cytosol is in the range of picomolar. When concentration of free zinc ions is higher than optimal, cells are able to transport them into subcellular store or release to extracellular space (Krężel and Maret 2016).

By no means, intensive application of ZnO NPs as biofungicide in the fields might increase the concentration of ZnO in the environment. Soil could be the major sink of NPs compared to atmospheric and aqueous ecosystems. NPs, released to soil may sorbed onto soil particles, may undergo degradation by biotic or abiotic processes, may be transported to groundwater. Once released to the environment, nanoparticles can accumulate in the ecosystems and can pose threats to living organisms. So, it is important to understand the behaviour of NPs in soil and evaluate the risks for arable soil ecosystems. It has been evaluated that environmentally non-toxic ZnO concentration in waste water must be lower than 0.3 μg/L (USA Standard) and 0.432 μg/L (Europe Standard) (Gottschalk et al. 2009). Considering that solubility of ZnO NPs in water is very low (7 mg/L) (Reed et al. 2012) and aggregation to microsize (1000 Å) is very fast, it is difficult to prognose accumulation of high amounts of ZnO NPs in the environment or living systems.

5.5 Conclusion and Prospects

The growing economy needs an ever-evolving technology to sustain the agriculture growth and to meet the needs of a large population. But the agriculture is faced with issues like climate change, reduction of agricultural land, and increasing population and food demands. To add to the problems, pests like insects, bacteria and fungi cause crop production losses, rendering it unsuitable for consumption. But the traditional and conventional pesticides and weedicides developed to tackle the pest problems are not able to keep up with the changing times and cater to the huge requirements. In fact, they do more harm than any good. Environmental pollution, antimicrobial resistance and low efficiency are currently the biggest side-effects of these existing pesticides.

The need for efficient and effective tools like nanotechnology comes into play in order to replace the existing traditional toxic chemicals in the agriculture. This chapter gives an insight of how nanotechnology can be a powerful tool in overcoming the disadvantages of the traditional pesticides. The chapter covers a wide range of nanomaterials and nanoparticles that have been studied for their antimicrobial effect against various plant pathogens. Along with the experimental results and data, the probable mechanisms of how these nanomaterials work against microbes have also been discussed. The key feature to note is that nanomaterials have been reported to work against antimicrobial-resistant microbes. It is also noteworthy that nanomaterials can also be biosynthesized which helps it to be eco-friendlier and a better alternative.

The versatility of nanomaterials has opened a wide horizon of new and better tools for agricultural use. The scope of nanotechnology is not only used in antimicrobial pesticides but also in nanobiosensors, pesticides degradation, micronutrient supply, detection and diagnosis of pathogens associated with different plant diseases, fertilizer and pesticides delivery systems, delivery of genetic materials for development of pest, pathogen and stress-resistant strain crop plants, and soil structure and remediation.

Nanotechnology is not completely a new technology. People have been using the technology in one or the other forms since ancient times. Albeit, the extensive understanding and study of nanotechnology has been done in recent times only. With the advent of nanotechnology, new possibilities have opened that need to be explored. Nanotechnology can be the future of the agriculture sector, providing better results and meeting the increasing demands of a growing population. Nanotechnology is a relatively newer tool still requires in-depth understanding and knowledge. Currently, there is a lack of knowledge of how size, shape, composition, concentration, agglomeration state, redox potential, catalytic activity and surface charge of NPs affect living organisms. Considering the environmental impact and fate of nanoparticles, it is important to know how nanoparticles affect all nature, starting from procaryotes (bacteria and other unicellular microorganisms), since they are the primary targets for being exposed to the man-made NPs after they are discharged into environment. Deep investigation about the effects of NPs on plant physiology, impact on animal health, soil structure and stability of ecosystems must be evaluated. So, the long-term effects of nanomaterials on the environment, plants and humans have to be studied carefully to assess all possible risks and toxic effects.

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Chapter 6
Biopolymeric Nanoparticles as a Nanocide for Crop Protection

Muthukrishnan Sathiyabama

Abstract Nanotechnology is gaining significant importance in agriculture for increased crop protection with the ultimate objective of enhanced total yield. Recently, numerous biopolymers such as chitosan, alginate, and glucan have been studied for the development of various materials due to their biocompatibility, biodegradability, low toxicity, and desirable functionality. These biopolymeric materials are important in agriculture because of their dual role—as the plant growth enhancer and plant protection agent. They also possess antimicrobial property. Various studies revealed that the application of biopolymer-based nanomaterials upregulates defense enzymes/genes in plants and protects crops from devastating pathogens. The unique properties of these materials at nanoscale level make them suitable for different application in achieving sustainability in agriculture. In this chapter, the synthesis, characterization, and application of biopolymeric nanomaterial as a nanocide have been explained.

Keywords Biopolymeric · Nanoparticles · Nanocides · Plant protection

6.1 Introduction

Field grown crops are frequently attacked by pathogens and cause various diseases. Disease decreases crop yield and quality and leads to considerable loss worldwide (Savary et al. 2012; Zhan et al. 2015). In conventional agriculture, pathogens and insect pests are controlled by application of fungicides and insecticides, which ultimately enters into the environment and causes deleterious effects (Stephenson 2003). Indiscriminate use of the chemical control increases resistance in the pests and reduces soil biodiversity by polluting the soil and water (Tilman et al. 2002). Also, the increasing demand of consumers for high quality, safe, and environment-friendly food products has encouraged the research for new biobased.

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In this direction, nanotechnology offers great promises in agriculture (Olivera et al. 2014; Wang et al. 2016). Nanotechnology uses the materials having one or more dimensions in the order of 100 nm or less (Auffan et al. 2009). As reviewed by many researchers, plant protection and nutrition nanomaterials hold great promise due to their novel size-dependent characteristics, high surface-to-volume ratio, and unique optical properties (Nair et al. 2010; Ghormade et al. 2011).

The physicochemical properties of nanomaterial can greatly vary from their bulk material and can generate unknown biological effects in living cells (Stampoulis et al. 2009; Saharan et al. 2015). These properties make them a suitable candidate material for controlled release of agrochemicals, stabilization of biopesticides, fabrication of biosensors for pathogen, and pollutant detection (Ghormade et al. 2011; Servin et al. 2015). Nanotools can be used for plant protection by combating the plant diseases either by controlled delivery of active ingredients or as diagnostic tool for disease monitoring. Nanomaterials enhance the ability of plants to absorb nutrients, enhance yield, or nutritional values (Tarafdar et al. 2013) and also offer protection (Park et al. 2006). Nanoagriculture involves the use of nanosized particles with unique properties with the aim to increase global food production and enhance food quality of commercially important crops through precision farming practices (Batsmanova et al. 2013; Shekon 2014; Prasad et al. 2014). In the area of plant pathology, nanotechnology can address the specific agricultural problems associated with plant-pathogen interactions and provide new solutions for crop protection. Several researches report the use of carbon-based and metal-based nanomaterials (Elmer and White 2016) for enhanced protection from phytopathogens. However, the potential adverse effects of these nanomaterials have raised serious questions about their application. Hence, the selection of nanomaterial may be critical as materials which are nontoxic, biocompatible, and biodegradable are desirable in agricultural applications. Nanoparticles prepared from biopolymer or natural sources possess advantages such as availability from replenishable resources, biocompatibility, biodegradability, and ecological safety (Anusuya and Sathiyabama 2015a). This book chapter describes some of the recent developments in biopolymer-based nanomaterial preparation and their potential applications in plant protection.

6.2 Synthesis of Polymeric Nanomaterials

Nanoparticle synthesis is carried by a variety of physical, chemical, and biological methods (Calvo et al. 1997; Divya and Jisha 2017; Sathiyabama and Parthasarathy 2016). Synthesis of nanoparticles involves two approaches. In top-down approach, the size reduction can be done by methods such as milling, high-pressure homogenization, laser ablation, chemical vapor deposition, sonochemical reduction, supercritical fluids, gamma radiation, and sonication, while bottom-up processes involve reactive precipitation and solvent displacement (Sasson et al. 2007; Charitidis et al. 2014). The chemical reduction in a liquid phase is the conventional method of NPs synthesis (Servin et al. 2015), and common reducing agents include citric acid, hydroxylamine, cellulose, sodium carbonate, etc. Polyvinyl alcohol and sodium polyacrylate are used as stabilizing agents to promote uniform particle size and distribution.

The materials like oxides, ceramics, silicates, magnetic materials, lipids, polymers, dendrimers, and emulsions can be are used to make NPs (Niemeyer and Doz 2001; Oskan 2006; Puoci et al. 2008). Polymeric NPs fabricated from natural and synthetic polymers through wet chemical methods are widely popular due to their stability and ease of surface modification (Wen et al. 2017). Controlled release of ingredients from the polymeric matrix is a useful character for developing polymeric NPs as agrochemical carriers. Numerous biopolymers such as starch, chitosan, chitin, glucan, and alginate are being used for the development of novel carriers for achieving the environmental sustainability (Babu et al. 2013). These biopolymers possesses the properties biocompatibility, biodegradability, non-toxicity and environmentally safe has helped to gain attention in various applications (Kole et al. 2013).

6.3 Characterization of Biopolymer-Based Nanocide

The physicochemical properties of synthesized nanoparticles can be characterized by various methods such as particle size, polydispersity index (PDI), internal, and surface morphology by dynamic light scattering, zeta potential (to identify the surface charge), functional group analysis through FTIR, scanning and transmission electron microscopy (SEM and TEM) (to measure size), X-ray diffraction (to analyze structure). PDI value of <0.5 represents the monodispersity of the nanoparticles. The zeta potential is an important parameter for judging the stability of nanoparticle suspensions. Nanoparticles mutually repel in solution if they possess either large negative or large positive charge, and so the nanoparticle suspension with a minimum zeta potential of ± 30 mV is considered as relatively stable (Zain et al. 2014).

6.4 Method of Nanoparticles Application

Delivery systems in agriculture are important for application of nanoparticles to improve plant growth and protection from disease. An application system for plant protection needs to focus on efficacy enhancement and spray drift management. Therefore, the mode of nanomaterial application decides how they interact with plants (Mohamad and Sakthi Kumar 2016). Conventional agriculture spraying involves covering of whole crop with chemical with more volume of solution. This is an easy method and costs very less for preparation. In contrast, the nanoformulations are expected to be in low volume and high-value application (Nair et al.

2010). The controlled delivery can be defined as technique that aims for measured release of necessary and sufficient amounts of agrochemicals over a period of time. This helps to achieve the fullest biological efficacy and to minimize its harmful effects (Tsuji 2001). For success of the controlled nanoparticulate delivery systems, the developer needed detail knowledge of the life cycle and the behavior of the pathogen or pest. Most of the researchers reported that foliar application and seed priming methods showed the best results in protecting crops from devastating fungal pathogens (Giannousi et al. 2013; Anusuya and Sathiyabama 2015c; Saharan et al. 2016). Seed priming of tomato and maize with Cu-chitosan nanoparticles increased seedling vigor index (Saharan et al. 2015; Choudhary et al. 2017a) and induced defense responses. Nanochitosan applied as seed treatment shown to be effective against seed-borne pathogens (Fahad et al. 2018). The combined (seed priming and foliar) application of Cu-chitosan nanoparticle to finger millet plants was better in controlling blast disease incidence when compared to foliar application alone (Sathiyabama and Manikandan 2018). Abdel-Aziz et al. (2018) reported that the foliar application of nanochitosan NPK fertilizer showed a significant increase in total saccharide content of wheat grains.

6.5 Mode of Entry

Due to Brownian diffusion, NPs are supposed to move to the various surfaces, and its mobility is predicted to have high efficiency of transport to collector surfaces, and their potential mobility is related to its surface properties (Remédios et al. 2012). The physiological investigations of foliar applied nanoparticles showed that the nanoparticles may enter through stomata and the cuticle structures (Eichert et al. 2008). Corredor et al. (2009) reported that the magnetic nanoparticles penetrated the pumpkin leaf through stomata and translocated to different regions of the plants. The translocation of nanoparticles from leaf to root after foliar application to watermelon was reported (Wang et al. 2013). In recent studies with Ag NPs, it was found that it was taken up in *Lactuca sativa* through stomata, and after entry, some of the particles were transformed in Ag ion (Larue et al, 2014). Eichert et al. (2008) studied factors like nanoparticles size and lateral heterogeneity of the stomatal foliar uptake pathway for aqueous solutes and water-suspended nanoparticles in *Allium porrum* and *Vicia faba*. The results have suggested that there are fundamental differences in the stomatal and cuticular foliar uptake pathway. Localization of chitosan nanoparticle in the cell walls of subsidiary cells in the lower epidermal peels of chitosan nanoparticle treated leaves of *Camellia sinensis* using FITC-tagged chitosan nanoparticle was reported by Chandra et al. (2015). The nanoparticles are also capable to enter through cell membranes of organisms, but their interactions with biological systems are relatively unknown. Recently, chitosan nanoparticles are found to be absorbed by the epidermis of leaves and translocated to stem reported and enhanced the growth and productivity of crop (Malerba and Cerana 2016).

6.6 Nano Particles and Composites of Biopolymers for Plant Protection

The polymers reinforced with small quantities of nanoparticles (up to 5% W/W) can be defined as nanocomposites. These nanoparticles improve the properties and performance of the polymer due to their high aspects of ration. Among the biopolymers, cellulose and chitosan have attracted more attention for fabrication of nanocomposites due to its versatile chemical functionality (Cao et al. 2011; Kashyap et al. 2015). Due to the properties like water holding capacity of nanocomposites, it can be used for various applications in agriculture.

6.6.1 NPs Based on Polymeric Materials

Polymer-based nanoformulations have received attraction due to its growth promoting, protective, and biodegradable nature (Kah and Hofmann 2014). Liu et al. (2001) reported that the NPs formulations based on polymeric materials polyvinylpyridine and polyvinyl pyridine-co-styrene were able to control a common brown rot wood decay fungus by slow release of the tebuconazole and chlorothalonil fungicides. Zheng and Shang (2005) used polymeric nanocapsules as a carrier for pesticides ivermectin and acetamiprid. Another study has used polymeric chitosan NPs incorporation of fertilizers. Corradini et al. (2010) achieved for controlled release of the NPK fertilizer sources such as urea, calcium phosphate, and potassium chloride. The polymers that are selected for field application should possess the properties like nontoxic biocompatible and biodegradable, and chitosan suits this condition.

6.6.2 Metal Complexed Chitosan Nanoparticles

The ability of chitosan to chelate metal ions such as Ag, Cu, and Zn makes it a potential candidate for making a perfect composite for different application. Saharan et al. (2015) used Cu–chitosan nanoparticles for plant growth promotion and antifungal activity in tomato. These nanoparticles were able to promote seed germination, seedling length, fresh, and dry weight in pot experiments. Also, in the case of *Alternaria solani* and *Fusarium oxysporum*, 0.12% concentration of these NPs was effective for disease spread. Chitosan-based zinc nanocomplex materials were evaluated against many bacteria and fungi and results indicated that it was better in case of controlling the bacteria when compared to fungus species (Wang et al. 2004). The preparation of the metal complexed chitosan nanoparticles is done by physicochemical method, namely ionic gelation method by the addition of copper sulfate and zinc sulfate during synthesis. In this method, the chitosan nanoparticles are formed by electrostatic interaction between charged amino group of chitosan and negatively charged phosphate group of thiamine pyrophosphate (TPP). Metal-based chitosan nanomaterials have been researched due to its dual activity as plant growth promoter as well as plant protection agent. Also, the encapsulated metals are less toxic due to its slow release. Brunel et al. (2013) reported the antimicrobial properties of Cu-chitosan nanoparticles against *Fusarium graminearum* through a strong synergistic effect between chitosan and copper. Foliar application of zinc complexed chitosan nanoparticles to *Zea mays* showed increased growth in zinc-deficient conditions (Deshpande et al. 2017). Saharan et al. (2015) reported application of Cu-chitosan nanoparticles to tomato plants showed increased seed germination, seedling vigor, and antifungal activity toward tomato phytopathogens such as *A. solani*, *F. oxysporum* under in vitro condition. They explained that the antifungal activity is due to more surface area and its positive charge which could interact with negatively charged cellular components of pathogenic fungi. Seed priming of maize with Cu-chitosan nanoparticles showed upregulation of amylase and protease activities (Saharan et al. 2016). Maize (*Z. mays* L.) plants treated with Cu-chitosan nanoparticle (0.04–0.16%) both under the pot and field condition showed enhanced plant height, stem diameter, root length and number, chlorophyll content, etc. (Malerba and Cerana 2018). Cu-chitosan and Zn-chitosan nanoparticles enhance various defense responses in maize plants when compared to their bulk counterparts (Choudhary et al. 2017a). Foliar application of Cu-chitosan nanoparticles induced antioxidant and defense enzyme activity in maize leaves along with a significant control in leaf spot disease was recorded under pot condition (Choudhary et al. 2017b). Cu-chitosan nanoparticle applied either through foliar spray or as combined method (seed priming and foliar spray) to finger millet plants showed induction of defense enzymes such as chitinase, chitosanase, β-1,3 glucanase, peroxidase, polyphenol oxidase, and protease and enhanced resistance to blast fungus *Pyricularia grisea* (Sathiyabama and Manikandan 2018).

In one study, the chitosan nanoparticles and chitosan silver nanocomposites (CAgNCs) were compared for their antifungal effects of against *F. oxysporum*, it was found that both the nanoparticles were able to stop the growth by disrupting the cell membrane. However, CAgNCs showed a significantly higher growth reduction along with the morphological and ultrastructural changes in the pathogen (Dananjaya et al. 2017). Also, a novel metal complexes containing chitosan with copper, zinc, and nickel were evaluated for antifungal activity against *Phytophthora capsici*, *Gibberella zeae*, *F. oxysporum,* and *Botrytis cinerea*, *the results suggested that* have metal significantly enhanced antifungal activity of the original chitosan (Liu et al. 2018). Huang et al. (2013) used chitosan/TiO_2 nanofilm to control southern corn leaf blight disease caused by *Bipolaris maydis*. Also, Li et al. (2016) reported that chitosan/TiO_2 nanocomposites inhibit the growth of rice pathogen *Xanthomonas oryzae*. Due to their biocompatibility, these kinds of nanoformulations have a potential to become the next generation of pesticides for plant protection (Brunel et al. 2013).

6.6.3 Nanoencapsulation of Growth Hormones by Chitosan Nanoparticle

Plant growth regulators such as auxins and gibberellins have broad application in agriculture and horticulture. A difficulty in using these PGRs is that it can readily degrade when exposed to light and temperature. Hence, these substances can be encapsulated in nanoparticles to improve their physicochemical properties. Gibberellic acid encapsulated with alginate/chitosan applied to *Phaseolus vulgaris* showed increased plant growth. Chitosan nanoparticle carrying gibberellic acid significantly increased the leaf size and chlorophyll content in the plant (Pereira et al. 2016, 2017).

6.6.4 Nanoparticles of Biopolymers

Nanoparticles prepared from enormous variety of materials pose potential adverse effect on biological systems and possible environmental toxicity (Prabhu and Poulose 2012). Because of their friendliness with the environment, natural biopolymers have attracted more attention. Along with eco-friendliness, they are nontoxic and low-cost materials with good physical and chemical properties (Mucic et al. 1998; Esumi et al. 2003). Chitosan nanoparticles are generally prepared through ionic gelation method using sodium tripolyphosphate (Du et al. 2009). Recently, it has been reported that the nanoparticles prepared from chitosan completely inhibit the plant pathogens as *Fusarium solani* under in vitro condition when compared to its bulk counterpart (Choudhary et al. 2017a). The probable mechanism of inhibitory effect was accounted to the particle size and zeta potential of chitosan nanoparticles. These results supported the future application of chitosan in nanosize as a natural antifungal agent with enhanced antifungal activity (Ing et al. 2012).

Chen et al. (2010) studied the antibacterial activities of chitosan nanoparticle and emphasized the antimicrobial activity depends on its zeta potential, which plays a significant role in binding with negatively charged microbial membrane. Chookhongkha et al. (2013) reported chitosan nanoparticle significantly delayed the mycelial growth of *Rhizopus*, *Colletotrichum*, and *Aspergillus niger* under in vitro condition. Van et al. (2013) reported that chitosan nanoparticle application significantly enhanced chlorophyll content in coffee leaves and showed positive impact on coffee seedling. It has been reported that when the leaves of *C. sinensis* are treated with chitosan nanoparticles treatment, it induced the activity of stress and defense-related enzymes like peroxidase, polyphenol oxidase, phenylalanine ammonia-lyase, β-1,3 glucanase, and catalase. The induction helped the plant to gain innate immune response (Chandra et al. 2015). Recently, Sathiyabama and Charles (2015) reported the synthesis of chitosan nanoparticle from the cell wall of *F. oxysporum* f. sp. *lycopersi* and investigated its impact on tomato plants. Their results demonstrated that chitosan NPs strongly induced resistance against early blight of tomato. Foliar application of chitosan nanoparticle to finger millet plants showed enhanced peroxidase activity through the induction of reactive oxygen species and delayed the blast disease development (Sathiyabama and Manikandan 2016). The chitosan nanoparticles are generally prepared by ionic gelation using sodium tripolyphosphate. Recently, from our lab, we reported the preparation of chitosan nanoparticles by biological method using the extracellular proteins of endophytic fungi *Penicillium oxalicum* which exhibited in vitro antifungal activity against some phytopathogenic fungi—viz., *P. grisea*, *A. solani*, *F. oxysporum* (Sathiyabama and Parthasarathy 2016). Kheiri et al. (2016) synthesised chitosan nanoparticle and tested its effect on the radial growth of *F. graminearum* under in vitro condition. They reported the chitosan nanoparticle at 1000–5000 ppm concentration inhibited the radial growth of *F. graminearum*. Manikandan and Sathiyabama (2016) evaluated chitosan nanoparticle for suppression of rice blast fungus under detached leaf condition and reported that the prepared NPs have the potential in suppressing blast disease of rice. Zhou et al. (2017) reported that application of nanochitin to tobacco improved the growth and protects from tobacco root rot disease. Chitosan nanoparticle treated wheat plants exhibited reduced head blight disease under greenhouse trails and the treated plants showed elevated levels of H_2O_2 accumulation (Kheiri et al. 2017). Siddaiah et al. (2018) reported that seed treatment of chitosan nanoparticle significantly enhanced seed germination % and seedling vigor index of pearl millet. They also reported that seed application induced systemic resistance to downy mildew protection under green house condition and the protection was modulated by NO generation. The treated seedlings showed upregulation of PAL, PO, PPO, catalase, SOD, PR1, and PR5 genes. Recently, it has been reported that chitosan nanoparticle functionalized with β-cyclodextrin showed sustainable release of active ingredient (Campos et al. 2018). Chitosan has emerged as the best carrier for agrochemicals due to its ability to function as a protective reservoir for active ingredients (Kashyap et al. 2015). When the antifungal activity of dispersed oleoyl-chitosan (O-chitosan) nanoparticles was checked against the few plant pathogenic fungi, it was found that plathogens like *Nigrospora sphaerica*, *Botryosphaeria dothidea*, *Nigrospora oryzae,* and *Alternaria tenuissima* have shown sensitivity to different concentration of chitosan; while *G. zeae* and *Fusarium culmorum* were chitosan-resistant. The antifungal assay negatively correlated the levels of unsaturated fatty acid present in plasma membrane of pathogen.

In one study, the nanocomposite films of methyl cellulose containing pediocin and zinc oxide nanoparticles have shown antimicrobial activity against *Staphylococcus aureus* and *Listeria monocytogenes* (Espitia et al. 2013). Pinto et al. (2013) have demonstrated the method for preparation of composite films of pullulan and Ag nanoparticles (NP), which has shown a promising antifungal activity of

A. niger. The results of their study have shown that this composite film shows strong inhibition of fungal sporulation, which was confirmed by disruption of the spores by SEM studies.

Glucans are the major cell wall polysaccharides present in many organisms and may report have suggested the important role of β-glucans in pathogen infection to induce systemic resistance in plants (Yamaguchi et al. 2000; Sriram et al. 2003; Shinya et al. 2006; Shetty et al. 2009; Sathiyabama and Balasubramanian 2018). It was also reported that it shows antifungal activity (Mauch et al. 1988; Sathiyabama and Balasubramanian 1998). We have reported earlier that β-D-glucan nanoparticle prepared from cell wall of *Pythium aphanidermatum* by precipitation method showed antifungal activity toward *P. aphanidermatum*, the causal agent of rhizome rot disease of turmeric (Anusuya and Sathiyabama 2014). High-level expression of defense enzymes in leaves and rhizomes of glucan nanoparticle treated turmeric plants were reported. The treated plants also showed a reduced rot disease incidence in field condition (Anusuya and Sathiyabama 2015a, b). The turmeric rhizome pretreated with glucan nanoparticle showed induced resistance against *P. aphanidermatum* infection under in vitro condition (Anusuya and Sathiyabama 2015b). In other studies, we have reported the foliar application of glucan nanoparticle significantly enhanced the plant growth in terms of plant fresh weight, leaf number, shoot height, and rhizome yield, and also offered protection to turmeric plants. The treatment not only promoted yield but also enhanced the curcumin content (twofold) in turmeric plants (Anusuya and Sathiyabama 2015a).

6.7 Conclusion

The past overuse of chemical pesticides and fertilizers in agriculture has resulted in environmental pollution, emergence of resistance in agricultural pests and pathogens, and also loss of biodiversity. Nanoscale materials have found their applications in crop protection due to their size-dependent qualities. Biopolymer-based nanoparticles have the potential to play a critical role in increased plant growth, rapid control of pest and diseases, protection from phytopathogens, their by enhancing food production, food security, and food safety. Recently, several approaches are being made to develop nanoformulations using biopolymer-based nanomaterials as agrochemicals around the world as an eco-friendly approach to protect crop plants from devastating pathogens. Hence, these biobased nanomaterials serve as nanocide for the control of phytopathogens to achieve sustainable agriculture.

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Chapter 7
Carbon Nanomaterials in Agriculture

Jagjiwan Mittal, Singh Osheen, Abhishek Gupta and Robin Kumar

Abstract Discovery of fullerenes, carbon nanotubes, and graphene in the short period of time and their unique properties led the boom in the applications of carbon nanomaterials (CNMs) on large scale in various industries. Potential applications of these materials in engineering, medical, environmental, and agricultural areas have attracted great interest these days. CNMs like carbon nanotubes, fullerenes, carbon nanoparticles, and carbon nanohorns among others have great application potential in agriculture. The current focus of agriculture research is a sustainable increase in crop production and protection, and CNMs can be very useful in achieving the goals. However, use of these materials also associated with their impact on the environment and other living organisms. Existing literature reveals mixed effects from CNM exposure on plants, ranging from enhanced crop yield to acute cytotoxicity and genetic alteration. This chapter describes the different types of CNMs and their use in different agricultural applications. The objective is to evaluate the current literature, including studies with both positive and negative effects of different CNMs on crop plants and associated organisms.

Keywords Carbon nanotubes · Graphene · Fullerenes · Plant growth · Plant protection · Toxicity

7.1 Introduction

7.1.1 Carbon Materials

Carbon is a peculiar element which forms a wide range of compounds and materials. Due to its catenation property, it is main element in compounds in organic chemistry and natural world. Besides forming the compounds with other elements,

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it also forms the carbon materials which contain >90% carbons. Carbon materials exist in both amorphous materials such as charcoal as well as crystalline-like graphite. Two oldest allotropes of the carbon comprise hard diamond and soft graphite. Both are used in a wide range of products, including consumer goods in various areas of human activity (Zaytseva and Neumann 2016). Carbon can polymerize at atomic level and hence can form long chains. It can form single, double, or triple linkage with other elements due to its four-valence state. It has comparatively small size than group IV elements and exceptional electron structure. Due to the above-specified properties, carbons show allotropy (different range of structures composed of same atoms).

7.1.2 Nanomaterials

Nanotechnology has contributed to many technologies and sectors. There is a rapidly increasing continuous demand of the nanomaterials in the commercial sector. It can be utilized to alter the strength, weight, conductivity, durability, reactivity, structure, etc. of the organisms and objects as per desired. These materials are present in very negligible quantity in natural state. So, they are engineered or synthesized in huge amounts and these engineered forms are then brought into implementation.

7.1.3 Carbon Nanomaterials

The carbon nanomaterials are a kind of nanomaterial that only comprises of carbon atoms. These materials have specifically earned great interest due to their exceptional structure. They are playing a vital role in microelectronics, gas storage, conductive composites, paints with higher durability, antifouling textiles, etc. (Mukherjee et al. 2016). They are now often termed as "wonder materials" due to their possible applications in various sectors. According to the latest research reports, application of carbon nanomaterials is going to increase in next few decades in a big way.

These nanomaterials are a class of engineered nanomaterials having exceptional electrical, mechanical, optical, and thermal properties which increase their applications in different areas (Bennett et al. 2013; Hurt et al. 2006; Srivastava et al. 2015). The synthesis techniques of various CNMs have progressed significantly over the last two decades. The Buckminsterfullerenes (C_{60}) were discovered in 1985 which was followed by carbon nanotubes in 1991. Single and multilayer graphene family was first prepared in 2004. These nanomaterials continue to dominate most applications in recent times (Bergmann and Machado 2015; Hong et al. 2015).

Depending on the heat of formation and pressure conditions, carbon forms thermodynamically favorable structures using sp^3 to sp^2 hybridizations. This produces materials such as nanodiamonds and graphene sheets (Mauter and Elimelech 2008). Carbon nanomaterials use the nanoscale quantum effects, the stability of resonance structures, and the tunable distinctive physicochemical properties (Mauter and Elimelech 2008). Since carbon-based nanoparticles exist in nature in very low quantity, therefore, they are synthesized according to their requirements. They have been proved to be very important due to their peculiar properties such as thermal and electrical properties specially conductivities, high mechanical properties, and excellent optical properties. Research has been carried out on carbon nanomaterials for their proper and efficient utilization for industrial applications. These materials are found to be having very wide scope in agriculture, ranging from plant growth promotion to its protection.

7.2 Carbon Nanomaterials Family

Carbon nanomaterials exhibit huge diversity in their structures, shapes, and sizes. As shown in Fig. 7.1, carbon nanomaterials family includes fullerenes, carbon nano-onions, carbon nanocones, carbon nanohorns, carbon quantum dots, carbon nanotubes (CNTs), carbon nanobeads, carbon nanofibers, nanodiamonds, and graphene (Baptista et al. 2015; Cha et al. 2013). Graphene is a two-dimensional structure having one atom thick sheet of sp^2 C-atoms in a hexagonal honeycomb crystal lattice. On the other hand, carbon nanotube is a tube shaped having sp^2 carbon atoms arranged in a rolled sheet. Carbon quantum dots are 5–10 nm-thick nanoparticles. Carbon nanomaterials are also known based on their geometrical structure. They can be tube shaped (carbon nanotubes), spherical or ellipsoidal (fullerenes), horn shaped (carbon nanohorns) etc. Brief description of each class is given below.

7.2.1 Carbon Nanotubes

Discovered in 1991, CNTs are cylindrical structures of carbon atoms that consist of rolled-up sheets of graphene. This is a carbon allotrope which is highly suitable for applications because of its exceptional properties. Carbon nanotubes may differ in length, diameter, number, and symmetry of the rolled graphite sheet (chirality). Based on their structure, CNTs may be classified into two main groups: single-walled nanotubes (SWCNTs) and multiwalled nanotubes (MWCNTs). SWCNT is a rolled-up sheet of single graphene in cylinder shape. It is having a diameter around 1–3 nm and a length of a few micrometers. On the other hand, MWCNT is having many graphene sheets rolled up in cylindrical shape. Its

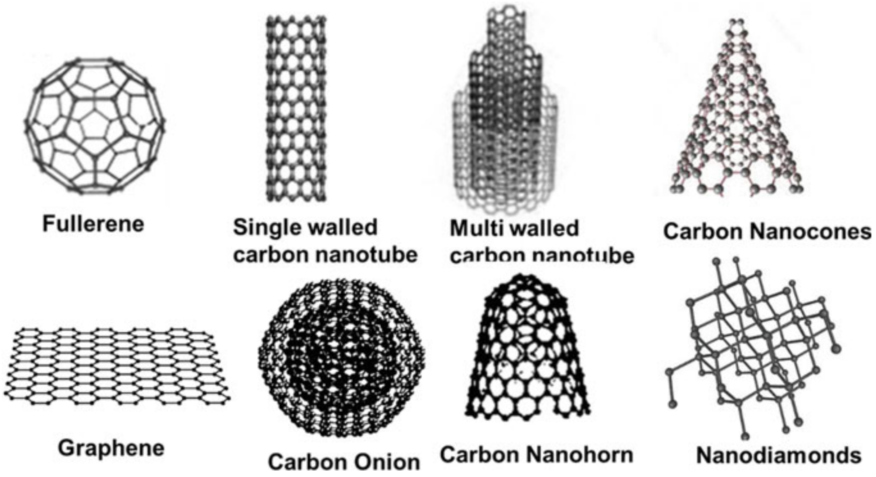

Fig. 7.1 Various types of carbon nanomaterials

diameter is usually between 5–100 nm and a length of around 2–10 μm. Synthesis of MWCNTs is comparatively easier and cheaper than SWCNTs (De Volder et al. 2013).

CNTs have extraordinary unique features, which have attracted scientists' attention. These nanomaterials have become increasingly popular in various fields simply because of their tiny size and unique optical, electric, and magnetic properties when used alone or with other metals. It possesses high thermal and electrical conductivity, high tensile strength, high flexibility, low thermal expansion coefficient, and good electron field emitting properties (Lota et al. 2007; Mittal and Lin 2017a, b).

7.2.2 *Fullerenes*

An allotrope of carbon synthesized first time in 1984, Buckminsterfullerene or Buckyballs are molecular forms of carbon. It exists in several forms like a hollow sphere, ellipsoid, tube, and many other shapes. Spherical fullerenes are also known as Buckminster fullerenes consist of hexagons and pentagons and they resemble the structure of a football. The carbon atoms in this structure are usually exist on the surface of the spheres (at the vertices of the hexagon and pentagon). Carbon nanotubes are usually called the tubular structure of fullerenes.

Fullerenes unique properties provide a range of application from biological to electronics because they:

- can behave as superconductors,
- are exceptional radical scavengers,

- possess high durability, and
- can be easily modified, enabling modification to their electronic structure, solubility, and physical properties.

7.2.3 Graphene

Graphene is a two-dimensional allotropic form of carbon which is formed by a single layer of carbon atoms. Having the sp^2 hybridization, carbon atoms joined together by σ and π bonds in a two-dimensional hexagonal crystal lattice with the distance of 0.142 nm between adjacent carbon atoms. Graphene is the basic element of some carbon allotropes, such as graphite and carbon nanotubes.

Some of the special properties of graphene are:

- Very high tensile strength because of the strength of covalent bonds between carbon atoms.
- High surface area because of its flat structure. Every atom is on the surface and is accessible from both sides, so there is more interaction with surrounding molecules.
- Easy to functionalize as carbon atoms are bonded to only three other atoms, although they have the capability to bond to a fourth atom.
- Very high thermal as well as electrical properties.

Due to its unique physical and chemical properties, Graphene is highly popular in the present decade among researchers and industries for applications (Kumar et al. 2017).

7.2.4 Other Carbon Nanomaterials

In additions to above, many other carbon nanomaterials are discovered in last two decades. Among them, carbon nano-onions, carbon nanohorns, carbon nanodots (Kushwaha et al. 2018; Suarez-Martinez et al. 2013), coated and/or filled carbon nanotubes (Mittal 2013; Mittal and Kushwaha 2015; Mittal and Lin 2011, 2013; Mittal et al. 2001), surface modified graphene, etc. are gained a lot of attention for various applications.

7.3 Carbon Nanomaterials in Agriculture

Providing food to continuously increasing world population is big challenge. Coupled with limited areas of arable land, and minimum negative impact on the environment is real headache for the world leaders and scientists. This problem can be solved using nanotechnology. It can increase the productivity of crops by using materials for plant growth and new nanomaterials-based fertilizers (Khot et al. 2012; Parisi et al. 2014). It can protect the plant using lesser pesticides (Kumar et al. 2013; Sarlak et al. 2014) and herbicides (Pereira et al. 2014) by using nanoencapsulated and slow-release formulation. Optimize agricultural practices by introducing precision farming (Auernhammer 2001).

Due to easy availability and interesting properties, in the last two decades, there has been great interest in the use of carbon nanomaterials (CNMs) in agriculture. It is estimated in one of the studies that maximum contributions of nanotechnology to agriculture will be provided by carbon-based nanomaterials (Gogos et al. 2012) and that may be in the form of additives or active components. Research has been carried out on using various carbon nanomaterials at different stages for the plant growth. The objective of this chapter is to discuss the contribution of carbon nanomaterials in agriculture including both positive and negative effects on plants.

7.3.1 Carbon Nanomaterials for Plant Growth

Carbon nanomaterials can play an important role in plant growth promotion as it can easily penetrate the cell membrane of plants. Several research studies are done and found that carbon nanomaterials can easily alter the physiological and morphological characteristics of the plant cells. They can enhance the crop yield when are used in fertilizers, plant growth stimulators, and as soil improvers. It has been observed in some studies that growth of plants is improved vastly when nanocarbon infused fertilizers were used. Studies have also shown that when seeds were cultured with carbon nanomaterials, germination of plants was increased. Some of studies and results on the use of nanocarbons in plant growth are described in the following sections.

7.3.1.1 Multiwalled Carbon Nanotubes

Nanotubes show very unusual properties that are useful for many applications. The outer diameter of these nanotubes ranges from 5 to 100 nm (De Volder et al. 2013). Inclusion of multiwalled carbon nanotubes into the plants seedlings has yielded positive outcomes on plant growth and development. The dispersion of MWCNT's in the growth medium showed better results compared to agglomeration in water. Results also indicated that the smaller and uniform MWCNT'S gave better results. However, the effect of MWCNTs on plant growth is concentration dependent. Low concentration of MWCNTs is more useful for plants than the higher concentration. It exhibited reverse effect on plants when the concentration was higher than the certain value (Srivastava et al. 2015). The MWCNT's are found to be better than other types of nanotubes because they can penetrate the harder seed coats by creating new pores or by perforation.

Some major studies have used hydroponics, agar, and soil culture as the medium of growth substrates and mainly focused on the germination and early growth phase. Various plant species like tomato (*Solanum lycopersicum*), wheat (*Triticum aestivum*), soybean (*Glycine max*), maize (*Zea mays*), mustard (*Brassica juncea*) black lentil (*P. mango*), garlic, barley, peanut, etc. had been studied with using MWCNTs. Some of the results on different plants are discussed below.

Water-soluble MWCNTs were used to see its effect on growth of maize crop. Diameter of the nanotubes used ranged from D: 10–20 nm, L: 10–30 μm with 20–50 mg L^{-1} concentration. Deionized water was used for germination as medium and exposed to the seeds for 5 days (Tiwari et al. 2014). These tubes showed different effect on root and shoot growth at different concentration. Their limited exposure to plant seeds resulted in increased growth and increased the water intake in plants as they entered the seeds by the formation of new pores.

Use of MWCNT's with the seeds of soybean, corn, and barley plants in agar medium resulted in increased seed germination. Growth rate was 50% more for barley and 90% for corn as compared to control, in addition to early activation of its growth. The root length was increased by 26% and the shoot length by 40%. The concentration of the MWCNT's used was 50, 100, 200 mg L^{-1} and the seeds were exposed to solution for 10 days (Lahiani et al. 2013). It was observed that for maize at 60 mg/L MWCNT's concentration, the nutrient such as calcium and iron uptake and the fresh biomass was increased by 43%. Another study has shown that the exposure of 2000 mg/L MWCNT's to ryegrass (*Lolium perenne*) increased the root length up to 19% (Lin and Xing 2007). In the case of mustard (*B. juncea*), oxidized MWCNTs of diameter 20 nm with 2.3–46.0 μg/L concentration have increased the shoot growth by 99% in 22 days (Khodakovskaya et al. 2012).

In tobacco plants, the MWCNT's with 5–500 μg/mL concentration were resulted in 60% more growth as compared to control (Khodakovskaya et al. 2011). The exposure of 50 μg/mL MWCNT in Murashige and Skoog (MS) growth medium resulted in 110% increase in fresh biomass of tomato seedlings (Khodakovskaya et al. 2011). However, there are some negative effects of using MWCNT's that include electrolyte leakage, membrane damage, DNA aberration, and cell death. Also, several times altering the morphological traits of plants changes their gene expression hence damages the DNA (Yang et al. 2017).

7.3.1.2 Single-Wall Carbon Nanotubes

The outer diameter of these nanotubes is 0.8–2 nm (De Volder et al. 2013) and the lengths range from 100 nm to several centimeters, depending on the desired application. Owing to their tunable properties regarding functionalization, and chirality, they can be used for agricultural and environmental applications. Many studies on the effect of carbon nanotubes on various aspects of plant were carried out.

Seed development is found to be depended on the amount of SWCNTs. It has been reported that the dose-dependent effect of SWCNTs for Salvia

(*S. macrosiphon*), pepper (*C. annuum*), and tall fescue (*F. arundinacea*) (Pourkhaloee et al. 2011), where 10–30 mg L^{-1} of SWCNTs improved the formation of seedling biomass, but use of 40 mg L^{-1} SWCNTs showed negative effects on seedling development. Similar response was observed for blackberry (*Rubus adenotrichos*) grown in vitro in a culture medium supplemented with SWCNTs-COOH. Different results were obtained while using the single-wall carbon nanotubes for short-term applications (24 and 48 h) on different plants. Nonfunctionalized SWCNTs suppressed root elongation in tomato (*Solanum lycopersicum*) but exerted stimulatory effects on cucumber (*C. sativus*) and onion (*Allium cepa*). Root elongation in lettuce (*Lactuca sativa*) was inhibited by SWCNTs functionalized with poly-3-aminobenzenesulfonic acid, while no effect was observed on cabbage (*Brassica*) and carrot (*Daucus carota*) (Cañas et al. 2008).

In one study with SWNTs, the growth of the rice plants was observed based on factors like germination rate, length of root, and shoot of the seedling, etc. The concentration of nanotubes used was 50 μg/ml and compared to control. The rate of gemination and water content was increased in treated seeds. Also, the treated seedlings were healthier and have well-developed root and shoots as compared to control seedlings (Nair et al. 2012).

The incorporation of the SWCNTs showed positive effect on the germination and growth of tomato seedlings. 10–40 mg/L of concentration of nanotubes (8 nm) was exposed to these seedlings in ultrapure water medium for 12 days. It enhanced the fresh biomass of tomato by 75%. The exposure of tomato seeds to 50 μg/mL SWCNT in MS growth medium resulted in 90% increase in fresh biomass (Khodakovskaya et al. 2011). For cabbage, carrot, cucumber, and onion, the size of nanotubes used was of 3 nm and dispersed in DI water for 2–3 days to obtain desired effects. The results were observed only on carrot and cabbage in terms of increased root length. There were no visible effects on growth parameters of cucumber and onion (Haghighi and da Silva 2014).

7.3.1.3 Graphene

The reports have suggested that graphene can penetrate the seed coat and the root tip cells. It also shows positive results only when used in specific concentrations and inhibits growth at higher concentration. The treated seedlings with graphene have germinated at a higher rate than normal seeds. When wheat seeds were exposed to 200 mg/L, hydrated graphene in water as a germination medium has shown faster growth and enhanced resistance to oxidative stress (Hu and Zhou 2014). The study has found that graphene has positively regulated the carbohydrate, amino acid, and fatty acid metabolisms that are critical for biochemical pathways involved in secondary metabolism, nitrogen sequestration, cell membrane integrity, permeability, and oxidation resistance.

In another study, tomato seeds were treated with 40 μg/ml of graphene. After exposure to graphene, the germination rate after 2, 4 and 6 days was increased by

26.6, 43.4, and 13.5%, respectively when compared to untreated tomato seeds. Germination factor was increased by 13% (Zhang et al. 2015).

The application of graphene and CNTs increased the germination rate of switchgrass seeds and led to an early germination of sorghum seeds (Pandey et al. 2018). The exposure of switchgrass to graphene (200 mg/l) resulted in a 28% increase of total biomass produced compared to untreated plants. Further, CBNs can significantly reduce symptoms of salt stress imposed by the addition of NaCl into the growth medium. Using an ion-selective electrode, concentration of Na^+ ions in NaCl solution can be significantly decreased by the addition of CNTs to the salt solution.

7.3.1.4 Fullerenes

When these structures are used in aqueous medium or when incorporated in soil, it did not show any effect on the germination of seedlings of many plants like wheat (*T. aestiva*), Arabidopsis (*A. thaliana*), rice (*O. sativa*), cucumber (*Cucumis sativus*), and gram (*Vigna radiata*). It was due to the selective permeability of the seed coat of the plants (Liu et al. 2010). It also showed no effect on the terrestrial plants and aquatic plants (Tao et al. 2015). Instead, root growth inhibition was observed in pumpkin (*Cucurbita pepo*) (Kelsey and White 2013). It was observed during study by Kole and coworkers that a fullerene derivative $C_{60}(OH)_{20}$, or “fullerol” treatment resulted up to 54% increase in biomass yield and 24% in water content. Increases of up to 20% in fruit length, 59% in fruit number, and 70% in fruit weight led to rise in fruit yield up to 128% in fruit (Kole 2013).

7.3.1.5 Coated and Uncoated Carbon Nanotubes

Poly-3-aminobenzenesulfonic acid (PABS) coated and uncoated nanotubes at 0, 160, and 900 mg/L concentration of coated nanotubes and 0, 104, and 315 mg/L concentration of uncoated nanotubes were used for exposure with six crop species (cabbage, carrot, cucumber, lettuce, onion, and tomato for up to 48 h). The result of the study has shown that there was an increase root length more in uncoated nanotubes as compared to coated nanotubes (Cañas et al. 2008). In another study, the impact of citrate coated water-soluble CNTs on gram (*Cicer arietinum*) after 10 days on exposure to 6.0 mg/mL was evaluated. They were able to visualize internalization of the CNTs by scanning electron microscopy and transmission electron microscopy; and hypothesized that once present inside the vascular tissue, the coated CNTs formed an “aligned network” that increased water uptake efficiency and resulted in plant growth promotion (Tripathi et al. 2011).

7.3.1.6 Nanocarbon Sol

In the experiment to study the physiological basis of potassium absorption in presence of nanocarbon sol, it was found that the nanomaterials showed a positive effect on the root growth of the tobacco (*N. tobaccum*) plant. When 5–20 mg/L of concentration was used in water as growth medium, there was an increase in root and shoot biomass and increased root length, and increased absorption of potassium was observed (Jian et al. 2014).

7.3.1.7 Other Carbon Nanomaterials

Increased growth in wheat was observed when exposed to 150 mg/L of water-soluble carbon nanodots (wsCND) for 10 days (Tripathi and Sarkar 2015). The microscopic analysis in this study has shown that wsCNDs can enter inside the plant cell and were nontoxic to plant at studied concentration. Treatment with water-soluble carbon nano-onions (wsCNOs) at 20 mg/L resulted in enhanced germination of gram seeds and also the better performance of plants in the pot experiments (Sonkar et al. 2012). The study has reported the potential of the wsCNOs as gentle growth promoter for crop plants. Carbon nanohorns have also shown a positive effect on the germination growth of crop species like barley, corn, rice, soybean, switchgrass, and tomato. They also shown 78% increase in callus growth in tobacco cell culture.

Use of 10–150 mg L^{-1} carbon nanoparticles in "biochar" after chemical oxidation in solution enhances the growth rate of wheat plants (Saxena et al. 2014). The concentration of CNPs used in this wheat plant growth study varied in the range from. The seeds treated with CNPs in this range showed higher growth rates, with the optimum growth found to occur with 50 mg L^{-1} CNPs, as compared with the control study.

In one study, water-soluble carbon nano-onions were used for the germination of gram seeds, for the initial 10 days only (Tripathi et al. 2017). Followed by transferring of 10 days, old seedlings were then transferred into the soil to complete their natural life cycle ($\sim$4 months). First-generation seeds harvested from the water-soluble carbon onions treated plants showed a significant increase in their yield and health with respect to their individual weight, overall dimensions, enhanced protein, stored electrolytes, and metallic micronutrient contents. In another study, same group of researchers have observed that the growth stimulation of gram plants depends on the morphology of water dispersible carbon nanostructures (Tripathi et al. 2016). Among these materials, 1D hollow nanostructures with the smallest diameters were found to be the best growth stimulators. The single-walled carbon nanotubes (SWCNTs) were found to be better promoters of plant growth than the open-ended multiwalled carbon nanotubes post 7 days. When compared, thick close-ended functionalized and annealed carbon nanowhiskers show lesser growth stimulation carbon dots (C-dots) show inferior performance.

The water uptake capacity, germination rate, shoot and root lengths, and chlorophyll and protein contents were significantly increased in *C. arietinum* plants using an aqueous colloidal dispersion ($\sim$230 nm average size) of the copper (Cu) nanoparticle (NP)-grown carbon nanofibers (Ashfaq et al. 2017), and can be used as control release tool for micronutrient. In one study, 20–30 mg/L carbon quantum dots synthesized from rapeseed pollen increased the production yield of Rome Lettuce (*Lactuca sativa* L.). Quantum dots were transported from nutrient solutions to vessels within the xylem of vascular bundles of both apoplast and cellular pathways along with the transpiration stream. The results demonstrated the potential ability of quantum dots act as labelling cells *in vivo*, and also affecting the plant physiology processes, and increasing the plant yield (Zheng et al. 2017).

7.3.2 Carbon Nanomaterials in Plant Protection

A wide variety of bacterial and fungal pathogens spoils crops. Among them, the most common bacterial agents are *Erwinia carotovora*, *Pseudomonas* spp., *Corynebacterium,* and *Xanthomonas campestris*. Fungal pathogens causing damages to various crops include species belonging to genera *Alternaria, Aspergillus, Cladosporium, Colletotrichum, Phomopsis, Fusarium, Penicillium, Phoma, Phytophthora, Pythium, Rhizopus* spp., *Botrytis cinerea, Ceratocystis fimbriata, Rhizoctonia solani, Sclerotinia sclerotiorum*, and some mildews. Some of these organisms are host specific whereas others affect a wide range of crop plants causing huge economic losses. Some pathogens produce toxic metabolites and adversely affect human health. Many of these agents enter the plant tissue over mechanical or chilling injuries and cause overwhelming losses (Levetin et al. 2016; Tournas 2005). With the estimated doubling in global food demand in next 50 years, huge challenges have been posed in food production.

Plant protection plays a significant role in achieving the better yield results. The major focus areas of plant protection are the development of integrated pest management (IPM), ensuring availability of safe and quality pesticides for sustaining crop production from the ravages of pests and diseases, streamlining the quarantine measures for accelerating the introduction of new high yielding crop varieties and eliminating the chances of entry of exotic pests. Different methods of plant protection have been reviewed by many reviewers that include chemical-based, biological, barrier methods, and based on animal psychology (Atwal 1986; Szekacs and Komives 2017). In the year 2000, the pesticide production was about three million tons of active ingredients worldwide (Tilman et al. 2002). It is reported that very small amount (less than 0.1%) of pesticide reaches the sites of action, due to loss of pesticide in air during application and as run-off, spray drift, off-target deposition, and photodegradation affecting both the environment and application costs (Castro et al. 2014; Pimentel 1995). With the growing demand of pesticide worldwide to control the pathogens and pests, there is an urgent need to tackle the excessive usage of pesticides and fertilizers by finding alternatives. The different carbon nanomaterials for plant protection or remediation of pesticides are discussed below.

7.3.2.1 Graphene

Many studies show the applications of graphene as an adsorbent for the removal of pesticides. It was found that for effective interactions between graphene and a pesticide, water with its polar structure plays an important role in mediating the adsorption of pesticides by graphene (Maliyekkal et al. 2013). The graphene has great adsorption capacities for pesticides (ranging from 600 to 2000 mg/g). Some researchers studied dehalogenation, halogenation, and removal of persistent halocarbon pesticides from water using graphene (Pei et al. 2013; Sen Gupta et al. 2015). Graphene and related carbon-based nanomaterials can adsorb contaminants with aromatic rings through π–π interactions (Smith and Rodrigues 2015). It can combine with other materials to improve pesticide adsorption capacity (Liu et al. 2013; Mahpishanian et al. 2015; Zhang et al. 2015). Graphene-coated silica (GCS) which is a highly efficient sorbent was used for removal of residual organophosphorus pesticides (OPP) from water (Liu et al. 2013). This study shows the mechanism of adsorption of OPPs on GCS is based on the electron-donating abilities of P, S, and N atoms and the strong π-bonding network of benzene rings.

7.3.2.2 Fullerenes

Plants produce antioxidants to protect themselves from both the ultraviolet light from the sun and the reactive oxygen species that are generated during the process of photosynthesis. Fullerenes and their derivatives are known to be very effective antioxidant and neuroprotectants (Dugan et al. 1997, 2001; Gharbi et al. 2005). The antioxidant, antiviral, and anticancerous activity of fullerols [$C_{60}(OH)_{20}$] have been ascribed to suppressed accumulation of superoxide and hydroxyl radical-initiated lipid peroxidation and free radical scavenging. The antioxidant property is because those fullerenes possess large amount of conjugated double bonds and low-lying lowest unoccupied molecular orbital (LUMO) which can easily take up an electron, making an attack of radical species highly possible. It has been reported that up to 34 methyl radicals have been added onto a single C_{60} molecule. This quenching process appears to be catalytic. In other words, the fullerene can react with many superoxides without being consumed. Due to this feature, fullerenes are considered to be the world's most efficient radical scavenger and are described as radical sponges (Krusic et al. 1991). The major advantage of using fullerenes as medical antioxidant is their ability to localize within the cell to mitochondria and other cell compartment sites, wherein diseased states the production of free radicals takes place.

Elevation of the antioxidant capacity of plants is expected to increase their tolerance to the development of necrosis caused by pathogens or abiotic stresses. Necrosis is the condition in plants in which there is degeneration of cells and tissue takes place. Necrosis weakens the plant and makes it more susceptible to other diseases and pests.

7.3.2.3 Carbon Nanotubes

The sustainability in pesticide application can be achieved by using MWCNT. The pesticides can be encapsulated into the CNT so that it will be released either gradually through the CNT walls, known as controlled release or diffusion, or when external conditions activate the capsule walls to break, melt, or dissolve. This results in the formation of encapsulated pesticide. This has been proved experimentally by some researchers. In one study, they encapsulated zineb and mancozeb into MWCNT-graft-poly(citric acid) (MWCNT-g-PCA) hybrid material (Sarlak et al. 2014). Mancozeb and Zineb are pesticides which protect many fruit, vegetable, nut, and agricultural crops against a wide range of fungal diseases. They converted bulk pesticide to pesticide nanoparticles. Effective parameters in the encapsulation process, such as pH, temperature, and time of stirring, were optimized via the UV−vis spectroscopy method. The effectiveness of encapsulated pesticide was studied with *Alternaria alternate* in laboratory condition. Results of study confirmed that pesticide encapsulated into CNT-g-PCA hybrid material is more stable and effective than bulk pesticide.

In one study, the effect of MWCNTs and C_{60} (fullerene) on the uptake of weathered chlordane or DDT and metabolites by *Cucurbita pepo* (Zucchini), *Zea mays* (corn), *Solanium lycopersicium* (tomato), and *Glycine max* (soybean) was investigated (De La Torre-Roche et al. 2013). After four weeks, Zucchini and tomato displayed no change, but corn and soybean showed reduction in biomass by C_{60}. MWCNT reduced chlordane, DDT, and metabolites accumulation in all crops. C_{60} blocked DDT and metabolites uptake complete in corn/tomato but raise 34.9% chlordane accumulation in tomato/soybean (De La Torre-Roche et al. 2013). These results show that the accumulation of pesticides depends on the crop species and nanomaterials characteristics and show the possibility of using engineered nanomaterials for food safety by promoting the phytoremediation.

7.3.2.4 Carbon Nanodots

It was observed that stress resistance ability of peanut plants is increased when it was grown with carbon nanodots aqueous solution at optimum concentration (Su et al. 2018). This also increased the output of peanuts by ~9%. Study showed the transfer of carbon nanodots from the roots to leaves through the xylem vessels of peanut plants. Hydrophilic groups on the carbon nanodots help in retaining and slowly release of micronutrients inside the xylem vessels of the peanuts. In another study with carbon quantum dots of ~5 nm size, it was found that they were capable to penetrate all parts of rice plants. They entered in the cell nucleus and resulted in loosening the DNA structure and increasing the thionin gene expression which enhanced the rice plant disease resistance ability. Carbon quantum was then degraded by the plants to form hormone analogues which promote the rice plant growth (Li et al. 2018). Carbon nanodots then degrade and form the plan hormone analogues which promote the plant growth, resulting in the 14.8% enhancement of the total rice yield.

7.4 Fate of Carbon Nanomaterials in the Environment

Many regulatory agencies have been focusing on the potential negative impacts of the nanomaterials in the environment that may outweigh the benefits provided by them. Compared to application-based research and development, studies on the ecotoxicity of CNMs are quite limited and involve a narrow range of test species and materials, growth media, and analytical techniques. Due to their unique and reactive properties, some infer that CNMs may have the potential to not only impact individual species but also to disrupt ecological dynamics (Nair et al. 2012). It has been reported that rice cell suspension (*Oryza sativa L.*) cultured with MWCNTs increased ROS and decreased cell viability (Tan et al. 2009). In the case of Arabidopsis cell culture, it seems that the CNTs induced very sensitive signals that resulted in defense responses in the cells causing cell death (Lin et al. 2009).

Human exposure to CNMs may occur through occupational settings or through indirect exposure from various environmental matrices such as air, water, and soils/sediments. The transport of the CNMs within environmental compartments is dependent on particle colloidal stability as well as their in situ transformation. The sorption properties and chemical transformation of CNMs may dictate mobility in soils and sediments and hence their bioavailability.

General conclusions on CNMs fate in the soil environment are difficult to draw because the process is dependent on multiple factors which are related to soil characteristics and composition, as well as CNM properties and the identity or susceptibility of potential receptors. Soil microbial communities have a direct impact on soil quality through processes such as nutrient cycling, decomposition of organic matter, and symbiotic relationships with terrestrial plant species (Kennedy and Smith 1995). Therefore, protection of soil microbial biomass and diversity is a major challenge in agriculture. Currently, limited information is available on the interaction between CNTs and soil microbial community (Simonet and Valcárcel 2009). Carbon nanomaterials may be directly toxic to soil microorganisms, may alter the bioavailability of nutrients, or may increase or reduce the toxicity of organic compounds and/or toxins (Dinesh et al. 2012). In addition, toxicity to plants may indirectly impact microbial communities.

7.5 Conclusions

Studies show that most of the carbon nanomaterials influence the crop plants. Small concentrations can induce physiological response, but higher concentrations can cause detrimental effects on plant or no effects. Nanocarbons can be used in the agricultural sectors for various applications but more studies are required to find out the behavior of these materials in environments. As a major challenge for the future, comprehensive studies on interaction of various carbon nanomaterials with living organisms and the environment will be important for both risk evaluation and the characterization of potential applications.

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Chapter 8
Nanotechnology and Entomopathogenic Microorganisms in Modern Agriculture

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Abstract The term entomopathogen refers to a microorganism capable of causing a disease to arthropods, leading to its death after a short incubation period. Nowadays few species of these microorganisms are known and being used to control a great variety of plague insects that affect the crops. At present, they turn out to be a quite profitable alternative in integrated pest management programs. But traditional IPM strategies are not enough in today's modern-day agriculture due to high rising world population. Therefore, along with the biocontrol, nanotechnology would provide a better option for sustainable management of insect pest. This chapter is focused on traditional strategies with entomopathogenic fungi and entomopathogenic nematodes that are used for the management of insect pests, their limitations, and potential of nanomaterials in improving its efficiency.

Keywords Entomopathogen · Nematodes · IPM · Nanoparticles · Nanocides

8.1 Introduction

Fungi, insects, and viruses are causal agents for the majority of the diseases in crop plants. The colonization of different parts of the plant by these organisms causes damage that moves from the loss of quality in the harvested products to the death of the plant. The control of pests and diseases depends on chemicals applications. However, their indiscriminate use has led to environmental contamination and generating the selection of highly resistant organisms. For these two reasons, new control strategies for pests and diseases are required. The use of microorganisms as

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biological control tools is an attractive alternative in modern agriculture (Ibarra et al. 2006). The application of this type of technologies is reflected in the changes observed in the global market of biopesticides. In 2013, sales of these inputs increased to US $1213 million, and it was expected that for 2017 they would reach a value close to US $3200 million (Markets and Markets, 2015 cited by Rivera-Méndez 2015). One of the main reasons for the interest in the potential of biological control as part of the integrated pest and disease management systems seems to respond to the demands of the markets and the awareness of the population about environmental protection and human health care, both themes present in the sustainable development agendas worldwide (Naranjo et al. 2015). The importance of these biological control is discussed further below.

8.2 Entomopathogenic Fungi in Agriculture

Entomopathogenic fungi have a great potential as controlling agents, constituting a group with over 100 genera and more than 750 species, disseminated in the environment and causing fungal infections to populations of arthropods (Pucheta-Díaz et al. 2006; Hasan 2014). According to López-Llorca and Hans-Börje (2001) the most important genera are *Metarhizium*, *Beauveria*, *Aschersonia*, *Entomophthora, Zoophthora*, *Erynia*, *Eryniopsis*, *Akanthomyces*, *Fusarium*, *Hirsutella*, *Hymenostilbe*, *Paecelomyces*, and *Verticillium*, while for FAO (2003) the most important genera are *Metarhizium, Beauveria, Paecilomyces, Verticillium, Rhizopus*, and *Fusarium*.

Entomopathogenic fungi are able to produce disease and death of insects (Asaff et al. 2002). This is the reason why they were the first biological agents to be used for the control of pests (Samson et al. 1988). Mechanisms for adhesion and recognition of host surface are present in most of these fungi, including synthesis of several enzymes (lipase/esterases, catalases, cytochrome P450s, proteases, and chitinases), specialized infectious structures (penetrant tubes or appressoria), and secondary metabolites helping infection. All these mechanisms provide entomopathogenic fungi direct adaptive response (Wraight et al. 2007).

Entomopathogenic fungi belong to 12 classes within six phyla of the kingdom fungi (AbdelGany 2015). Fungi that are pathogenic to arthropods are found in the divisions Ascomycota, Zygomycota, and Deuteromycota (Samson et al. 1988), as well as Oomycota and Chytridiomycota (Shahid et al. 2012). Many of the entomopathogenic fungi known so far belong to either the class Entomophthorales in the Zygomycota or the class Hyphomycetes in the Deuteromycota.

Entomopathogenic fungi, unlike other entomopathogenic agents, have unique invasion mechanisms (Haraprasad et al. 2001; Charnley and Collins 2007). There is no need of whole fungi mycelium ingestion by the insect to start infection, and can be initiated by single contact of spores with the buccal apparatus, the intersegmental membranes, spiracles, and other parts of the insect body (Jeffs et al. 1997; Kershaw and Talbot 1998). These fungi initiate their infective process and pathogen–host association by forming the germinal tubules and sometimes the appressorium (which serves to anchor the spore), with which it exerts a pressure toward the interior of the insect facilitating the invasion of the fungus (Asaff et al. 2002; Barranco-Florido et al. 2002). In synthesis, according to Carreño (2003) the mechanism of action is divided into three phases: (1) adhesion and germination of the spore on the cuticle of the insect, (2) penetration, and (3) development and growth of the fungus, which usually results in the death of the insect.

After the cuticular penetration, entomopathogenic fungi proliferate inside the insect and initiate the mycelial growth using their hyphal bodies that invade diverse structures such as muscular tissues, fatty bodies, Malpighi tubes, mitochondria, hemocytes, endoplasmic reticulum, and nuclear membrane (Pucheta-Díaz et al. 2006). Finally, the hyphae penetrate the cuticle from inside the insect and emerge to the surface, initiating the formation of spores when adequate conditions such as relative humidity and temperature are present (Gillespie and Claydon 1989).

Entomopathogenic fungi combined with predatory insects can be a viable alternative for biological control of insects; their compatibility was demonstrated in a study conducted with *Metarhizium anisopliae* and *Beauveria bassiana* in the control of *Podisus nigrispinus*, whose infestation occurred by various means of contact such as fungus spread or spraying, walking on plant surfaces, and ingestion of contaminated prey (Goettel et al. 1990; França et al. 2006).

Biotic and abiotic factors are important for the epizootic manifestation of entomopathogenic fungi to take place. The susceptibility and the relation to the hosts are linked to the nutrients present in the insects, which are the means for the propagation, dispersion, and persistence of the fungi. The spores of entomopathogens have specific water and temperature requirements, as well as other environmental factors acting together as inducers for the activation of receptors present in the pathogen, which allow them to carry out the infective process on the host (Hajek 1997).

Several studies demonstrated the effectiveness of the entomopathogen fungi in the control of pathogens. *Cladosporium*, *Trichoderma*, *Diaporthe*, *Phoma*, and *Alternaria* have been reported by Amatuzzi et al. (2018) as antagonistic to phytopathogenic fungi. Some fungi species such as *Cladosporium* sp., *Aspergillus* sp., *Nigrospora* sp., *Fusarium* sp., *Trichoderma* sp., *Chaetomium* sp., *Alternaria* sp., *Paecilomyces* sp., and *Phyllostica* are often isolated from several plant species as endophytic fungi (Gazis and Chaverri 2010; Kurose et al. 2012; Parsa et al. 2016). Plant defense is enabled and resistance is induced by *Trichoderma* (Verma et al. 2007; Bailey et al. 2009; Kurose et al. 2012), while control of plant-parasitic nematodes can be achieved by using some species of *Fusarium* and *Purpureocillium* (*Paecilomyces*) (Mendoza and Sikora 2009). Secondary metabolites displaying antimicrobial and antifungal properties from *Aspergillus*, *Penicillium,* and *Chaetomium* are produced massively (Li et al. 2011; Wang et al. 2012; Jouda et al. 2014). Khosravi et al. (2015) under controlled conditions reported a relatively high efficacy of *B. bassiana* isolates on *Arge rosae* (Hymenoptera; Argidae). The wild-strain *Trichoderma atroviride* T23 was successfully used for chalk brood disease pathogen (*Ascosphaera apis*) control in honey bees (Xue et al. 2015). Hussein et al. (2013) reported a mortality rate higher than 90% after treating the third-instar larvae of *Spodoptera littoralis* (Noctuidae: Lepidoptera) with a new lineage of *Purpureocillium* sp. (*Paecilomyces* sp.) (CCM 8367) in a suspension concentrated at 5 × 10^7 conidia ml^{-1}.

The effectiveness of three entomopathogenic fungi [*Beauveria bassiana, Metarhizium anisopliae,* and *Purpureocillium* (*Paecilomyces*) *fumosoroseus*] was evaluated for the control of pests in vegetable crops, emulsified in diatomaceous earth in a 1:10 ratio. The fungi were applied at a concentration of 1.2 × 10^{12} spores ha^{-1} generating mortality higher than 80% after 72 h of application (García-Gutiérrez and González-Maldonado 2010). Mata and Barquero (2010) evaluated the feasibility of production of *B. bassiana* in liquid medium for the purpose of controlling the coffee berry borer (*Hypothenemus hampei*). They found that the best growth of the fungus occurs on the fourth day in a medium consisting of sugar, yeast extract, and peptone, without being affected by the initial pH or the temperature of 28 °C; the mortality was 86.7%. Posada and Lecuona (2009) evaluated the effectiveness of 259 isolates of *B. bassiana* obtained from soil dead ticks and fungal collection for the control of *Boophylus microplus* and found that the concentration for 98 most virulent isolates was 1 × 10^7–1.15 × 10^7 conidia ml^{-1}.

Control of the mite *Psoroptes ovis* with *M. anisopliae* was performed *in vitro* and *in vivo* in preparations with diatomaceous earth and generates infection more than 90%. That's why it was recommended for the control of this ectoparasite (Abolins et al. 2007). The effectiveness of 29 isolates of *M. anisopliae* and 30 of *B. bassiana*, on workers and males of *Vespula germanica* at a concentration of 0 to 1 × 10^8 conidia ml^{-1} in the aqueous sugary medium were evaluated. Mortality that ranged from 70 to 97% was generated by *B. bassiana,* and results concluded that at a concentration greater than 10^7 conidia ml^{-1} the mortality of the population was higher than 90% (Merino et al. 2007). The pathogenicity of *M. anisopliae* and *B. bassiana* was evaluated in the control of the eggs of the tomato moth (*Tuta absoluta*), finding that the isolates of *M. anisopliae* Qu-M558 and *B. bassiana* Qu-B912 were the most effective, and achieving a mortality of 80 to 60%, respectively (Rodríguez et al. 2006). These all studies have proven the importance of entomopathogenic fungi in pest control in sustainable agriculture. As it has revolutionized the other sectors like drugs and electronics nanotechnology has the potential to improve the efficiency of the biological control. The role of nanotechnology is discussed further.

8.3 Nanotechnology and Entomopathogenic Fungi

Nanotechnology is based on the synthesis of nanoparticles of size ranging from 1 to 100 nm that can be manipulated for several applications. Until now, numerous nanoparticles of particular shapes and sizes have been synthetized and they are useful for drug delivery, pharmaceutical purposes (Devi et al. 2017), agriculture (Bhagat et al. 2015), and some other fields.

As discussed in other chapters of this book, through nanotechnology pesticides can be delivered to a specific target, seed germination and plant growth are promoted, crop yield is improved, pathogens can be efficiently controlled in the field and then products are stored (Kitherian 2017) (Fig. 8.1). Some studies with entomopathogenic fungi are discussed below.

Recently AgNPs for insect pest control using *Bacillus thuringiensis* Kurstaki (Btk) were synthesized. The NPs were obtained either from the supernatant or the pellet of various concentrations of Btk culture; and were characterized by UV–Vis spectrophotometry and dynamic light scattering (DLS). AgNPs production was successful at 20% supernatant or pellet treatments of Btk, being the size of particles around 85 nm for both. Two important pathogens were selected for this study. One was the cabbage looper, *Trichoplusia ni* (Hübner) (Lepidoptera: Noctuidae); that is a widespread, polyphagous species, whose larvae are a serious pest of Brassica crops and to greenhouse crops such as tomato, cucumber, and bell pepper (Sarfraz et al. 2011). The second was the black cutworm *Agrotis ipsilon* (Hufnagel), a major pest on golf course greens, trees, and fairways (Potter 1998). Both Btk-synthesized from Bt supernatant (AgNPs) or Btk-synthesized from Bt pellet

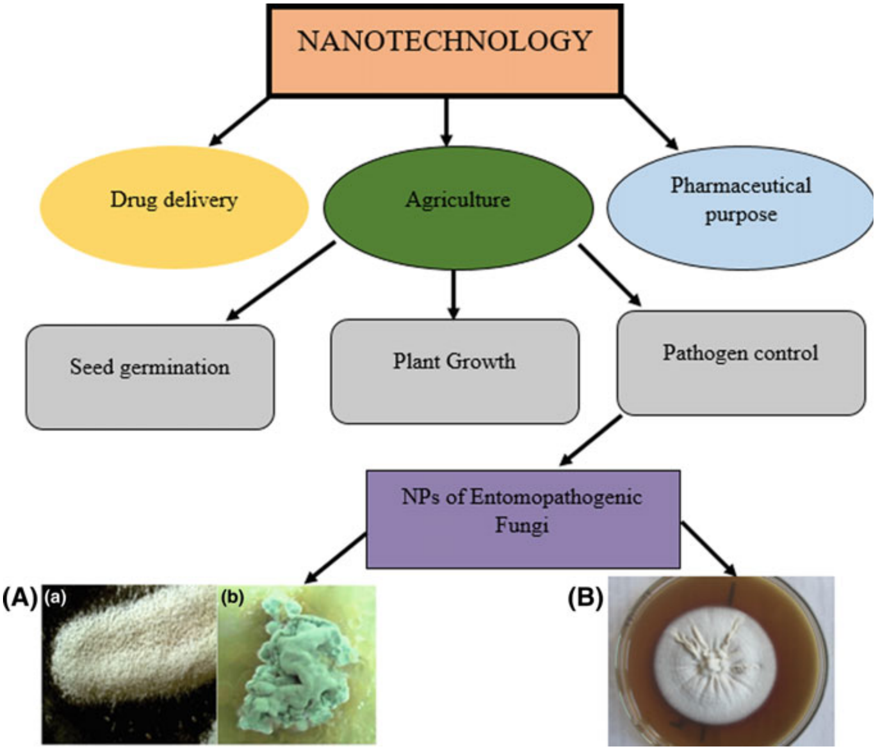

Fig. 8.1 Applications of nanotechnology, (A) *Metarhizium rileyi* (Farlow) Samson, (B) *Beauveria bassiana* (Balsamo) Vuillemin

(AgNPp) were significantly more virulent to larvae of *T. ni* than to *A. ipsilon* (Sayed et al. 2017).

The synthesis of AuNPs is not well-known in fungi unlike bacteria (Rai et al. 2013). In fungi, less than 30 species are identified for this matter, such as *Alternaria alternata*, *Colletotrichum* sp., *Neurospora crassa*, *Pseudomonas aeruginosa*, and some others (Kitching et al. 2015). Raheman et al. (2011) were successful in the synthesis of AgNPs from *Pestalotia* sp., an endophytic fungus isolated from *Syzgium cumini* (L.) leaves. They obtained spherical and polydispersed AgNps with a size of 12.4 nm. Another fungus used with this purpose was *Trichoderma reesei* because of its capacity to produce extracellular enzymes (Vahabi et al. 2011).

The fungi have also been reported as good agents for the synthesis of metal sulfide NPs, such as cadmium sulfide (CdS), zinc sulfide (ZnS), lead sulfide (PbS), and molybdenum sulfide (MoS) that can be produced extracellularly when the fungus *Fusarium oxysporum* is exposed to aqueous solutions of metal sulfate (Ahmad et al. 2002). Crystals of strontium carbonate ($SrCO_3$) were also obtained from fungi incubated with aqueous Sr^{2+} ions; thus, secretions of proteins during *F. oxysporum* growth may modulate the morphology of strontianite crystals (Rautaray et al. 2004).

Trichoderma viride, an entomopathogenic fungus, was used to produce a bioinsecticide by the synthesis of titanium dioxide nanoparticles (TiO_2NPs) (Kamaraj et al. 2018). *Helicoverpa armigera*, a highly polyphagous species reported feeding from more than 60 species of cultivated and wild plants (Fitt 1989; Pogue 2004) was used to test the synthetized TiO_2 NPs from *T. viride*. The evaluation of the NPs was done for larvicidal, antifeedant, and pupicidal activities against the pathogen being 100% effective in the first and second instar and 92.34% in the third instar at 100 ppm; for antifeedant and pupicidal activities the effectivity was 100% with 100 ppm of the TiO_2NPs. These nanoparticles were significant inhibitors of the pathogen *H. armigera* (Kamaraj et al. 2018).

A study with titanium NPs (TiNPs) was done by Yosri et al. (2018). The NPs were mycosynthesized using the fungus *Metarhizium anisopliae* unirradiated and irradiated (0.4 KGy), and the insecticidal activity was evaluated against *Galleria mellonella* larvae. This caterpillar, due to its easy handling and low-cost of maintenance, is widely used as host for testing fungal virulence and antifungal agents (Renwick et al. 2006; Mylonakis 2008). The combination of irradiated *M. anisopliae* with its mycosynthesized TiNPs resulted in highest effect in larvicidal activity. Irradiated *M. anisopliae* cells and their mycosynthesized TiNPs showed a synergic effect, with a synergistic factor (SF) of 1.6 for LC50 and 4.2 for LC90. Reduction of the likelihood of increased insect resistance to entomopathogenic fungi was the purpose to be achieved through this study (Yosri et al. 2018).

The fungus *Metarhizium rileyi* (Farlow) Samson also known as *Nomuraea rileyi* (Farlow) Samson is pathogenic for more than 30 Lepidoptera larvae species, mainly in wet conditions (Devi et al. 2003). This fungus has been isolated fundamentally from the bodies of dead insects and the cultivated soils (Bing et al. 2008), being associated with important pests in maize fields like *Spodoptera frugiperda* (Wyckhuys and O'Neil 2006). *M. rileyi* has not yet been broadly used as a mycoinsecticide, even though its potentiality as a biological control agent is widely acknowledged (Faria and Wraight 2007). In recent years, there have been advances in mass reproduction, but it is still necessary to continue working in that direction (Méndez et al. 2007; García et al. 2006). Chitosan is a chitin derivate and have been proved to have insecticidal activity against some plant pests (Sahab et al. 2015). Nanoparticles of chitosan with *M. rileyi* were studied to control *Spodoptera litura* (Chandra et al. 2013). Chitosan NPs coated fungal metabolites were more effective in the control of *S. litura* than uncoated fungal metabolites and fungal spores. Differences were found for the age of the insect, when the instars were older the mortality decreased and adult longevity increased.

A nano-entomopathogenic fungus *M. rileyi* was tested under field and laboratory conditions against the potato tuber moth *Phthorimaea operculella* (Sabbour and Solieman 2015) and results showed that the effects on egg laid/female were significantly decreased and the percentage of malformed adults after the application of the nano-fungus was until 97%. Namasivayam et al. (2013) studied the compatibility of some metal nanoparticles and *M. rileyi*. Effects on post treatment or viability of *M. rileyi* were not observed when AgNPs were used, and when not, the concentration of the fungus was the same to that with chitosan-coated silver nanoparticles treatment. Normal spore germination of the fungus was shown either for free silver or chitosan-coated silver NPs treatment at all the concentrations used; also, in all the concentration of free and copper nanoparticles significant inhibition was detected in spore germination.

The fungus *B. bassiana* is known as an entomopathogen since 1835 when it was discovered causing the death of silkworms (Commonwealth Mycological Institute 1979). It is found naturally in soils or on various orders of insects (Coleoptera, Diptera, Heteroptera, Homoptera, Lepidoptera, and Thysanoptera) as well as on tetraniquid mites, so it has been used to control pests of these orders in various countries. As an example, it has been used for the control of *Bemisia tabaci* (Genn.) (Landa and Jiranova 1989; Kurogi et al. 1993; Wright and Knauf 1994), *Dialeurodes citri* (Ashm.) (AviDzba 1983) and *Trialeurodes vaporariorum* (Westw.) (SüKhova 1987; Dirlbek et al. 1989). Qamandar and Shafeeq (2017) used *B. bassiana* for the biosynthesis of AgNPs based on the extracellular secretion of enzymes that can be simply processed by cells filtration and enzyme isolation for synthesis of nanoparticles from cell-free filtrates. The AgNPs were synthetized at room temperature and they were stable without the use of toxic chemicals for capping. In this study, authors found that pH could affect the NPs synthesis in *B. bassiana*; thus, the structures can be affected at lower pH and proteins are denatured with activity losses (Banu and Rathod 2011), maybe because the enzyme catalyzing the synthesis (reductase) is deactivated progressively when conditions are alkaline (Qamandar and Shafeeq 2017). Kamil et al. (2017) evaluated 25 isolates of *B. bassiana* against the aphid *Lipaphis erysimi* of *Brassica* sp. and used them for AgNPs production by a cell filtration method, obtaining the higher production in two isolates (B4 and B13). Significant mortality of *L. erysimi* caused by AgNPs particles of all isolates was found, but B4 and B13 showed the maximum values (60.088%).

Rice weevil, *Sitophilus oryzae* Linn. (Coleoptera: Curculionidae) is a pathogen of stored products such as rice and other grains (Kent 1983). The damage on the grain endosperm caused for the adults leads to reduction in the carbohydrate content; meanwhile, the larvae prefer the grain germplasm, thus lessening a great percentage of the proteins and vitamins (Belloa et al. 2000). Sabbour and Solieman (2015) studied the efficacy of NPs of *B. bassiana* and *M. anisopliae* to control *S. oryzae*, and the infestations were significantly decreased after the—nano—*B. bassiana* and *M. anisopliae* were applied compared to the control. The emerged adults were significantly decreased in the store in the treated bags.

8.4 Entomopathogenic Nematodes in Agriculture

8.4.1 Nematodes

Nematodes are one of the most distributed group of animals in the world, from fresh or saltwater (water films of 1–5 μm thick) or in the soil. Many species are free-living, feeding on bacteria or fungal spores, whereas others are predatory or parasitic in habit. It is estimated that around one million nematode species are present in the planet, but only 27,000 species have been described in the phylum Nematoda (Quist et al. 2015). Nematodes are simple organisms. To sense the environment, nematodes use chemical sensory mechanisms associated with their cuticle. These invertebrates have an appearance similar to a worm but are taxonomically distinct from them. They are composed approximately one thousand somatic cells in adult stage and its size is variable from 100 μm to 8 m; however, the majority of them are less than 1 mm in length and from 15 to 20 μm in diameter (Quist et al. 2015). Body cylindrical, elongated without limbs protruding and covered by an elastic cuticle usually marked by striations, that is associated with locomotion. The cuticle of nematodes is formed from a sheet of cells called epidermis (exoskeleton), and during their juvenile stage most of them molt the cuticle four times (J1–J4) before they become adults (Bird and Bird 1991a; Perry and Moens 2011). The cuticle consists mainly by collagen, plays an important role in the maintenance of hydrostatic pressure, due to its permeability, which allows the passage of water and ions through it. Also, the cuticle is of a taxonomic nature, due exhibits great diversity (Perry and Moens 2011).

The muscles of the nematodes are located below the epidermis aligned longitudinally inside the body, and two nerves (dorsal and ventral) located near the head are those that activate these muscles (Bird and Bird 1991b). In the head, nematodes have sense organs (e.g., amphids) and the mouth, then a muscular pharynx that leads to a gut cavity and finally to anus. The nutrients and waste of these organisms are stored in the pseudocoelom, and subsequently eliminated by the excretory system because they do not have a vascular system for the distribution of digested food. In addition, they lack a respiratory system for the uptake or distribution of oxygen (Bird and Bird 1991c).

8.4.2 Entomopathogenic Nematodes as Biocontrol Agents

Nematodes cause various diseases in humans and animals; in addition, in the agricultural area they can regulate the abundance of plague insects, where their relationship with arthropods is diverse. In this regard, thirteen different suborders of nematodes associated with insects have been reported (Viglierchio 1991; Blaxter 2011). Entomopathogenic nematodes (EPN) have many of the desirable characteristics of insect parasitoids. *Deladenus siricidicola* was the first EPN used for biological control of insect, and subsequently several EPNs belonging to the genera *Heterorhabditis* (Family: Heterorhabditidae) (Poinar 1976) *Steinernema* (Travassos 1927) and *Neosteinernema* (Family: Steinernematidae) (Nguyen and Smart 1994) were reported with biological and economic importance in the control of pests, specifically of the orders Coleoptera, Dictyoptera, Lepidoptera, Hemiptera, and Orthoptera (Georgis et al. 2006; Sepulveda-Cano et al. 2008).

The invasive stage of nematode is third instar larva that survives only under high humidity conditions. Dauer larva is ingested by the host insect, penetrate the anterior part of the alimentary canal, and invade the hemocoel, where they reproduce. The eggs hatch inside the female and the released juveniles feed on the mother (Srivastava 2004; Griffin et al. 2005; Rao and Tanweer 2011). Once EPNs have penetrated the body of insect larvae, they release mutualistic bacteria symbionts that kill the host within 48–72 h; after that, they develop, reproduce, and complete its cycle with one to three generations depending on the size of the host (Georgis and Gaugler 1991; Laznik and Trdan 2013). The EPNs are found naturally in the soil environment and contribute to the insects' control (Poinar 1979; Petersen 1985).

There is a relationship of EPN with bacteria, where each species of nematode is tightly associated with a certain species or subspecies of members Enterobacteriaceae family. Nematodes act as vectors, transporting, and inoculating the bacteria. In this sense, some EPN species of the Steinernematidae family have associated with symbionts *Xenorhabdus* spp. (20 species), contained in a special intestinal vesicle of *Steinernema* (Bird and Akhurst 1983); while nematodes of the family Heterorhabditidae have the bacteria *Photorhabdus* spp. (three species), contained in the anterior part of the intestine in *Heterorhabditis* (Ciche and Ensign 2003). This apparently symbiotic relationship between the nematode and its bacteria has been considered the main factor responsible for the death of the insect (Poinar 1979).

8.4.3 Entomopathogenic Nematodes and Nanotechnology

Although nanoparticles have reported to play very important role in pest control (Kim et al., 2012), still it is not completely clear if they have any synergistic, preferably, or antagonistic influence on popular biological control agents, such as EPNs (Kucharska et al. 2011a, b). Taha and Abo-Shady (2016) studied the effect of different concentrations (1500, 500, 200, 40, and 20 ppm) of silver nanoparticles on mortality of EPNs *Heterorhabditis indica*, *Steinernema arenarium*, and *Steinernema abbasi* and its effect on the pathogenic properties of EPNs for *Galleria mellonella*. They have reported that mortality percentage of EPNs depended on nano-Ag concentrations and the exposure time. There was a slight effect on pathogenicity, while there was a significant effect on EPNs reproductivity with the two concentrations assayed (500 and 1500 ppm).

In another study, it was reported that mortality of *Steinernema feltiae* (Owinema biopreparation) and *Heterorhabditis bacteriophora* (Nematop biopreparation), depends on nano-Ag concentrations and the time of dauer larva contact with them. Likewise, they analyzed the concentrations of nano-Ag that did not significantly affect the different pathogenic properties of the EPNs (Kucharska and Pezowicz 2009; Kucharska et al. 2011b).

On the other hand, the effect of different concentrations of nano-Au on the mortality *Steinernema feltiae* from Owinema biopreparation has been also reported. It was found the mortality of the larvae depends on different concentrations of nano-Au and also the time of contact. Mortality of *S. feltiae* increased when Au concentration was higher and at 5 ppm caused 78% mortality, while 0.5 ppm caused only 9% (Kucharska et al. 2011a).

In one study, the effect of copper nanoparticles on the mortality of *S. feltiae* and its ability to control *Alphitobius diaperinus* population were analyzed. It was found that mortality of *Steinernema* larvae depends on the exposure time with nano-Cu and solution concentrations. It was also found that high Cu concentrations may affect their ability to enter and multiply in the insect (Kucharska et al. 2014). Under laboratory conditions, control of the lesser mealworm *Alphitobius diaperinus* using EPNs combined with nanoparticles was studied. The *Steinernema feltiae* and *Heterorhabditis bacteriophora* were earlier exposed to Ag, Au or Cu nanoparticles and then used for pest control. Most of nematodes that survived the exposure of nanoparticles developed in *A. diaperinus* larvae, pupae, and adults. Significant differences for various host growth stages were found in the sensitivity and susceptibility to penetration by parasites. The studied nematodes and nanoparticles resulted in higher mortality and extensity of infection in host larvae, from 12 to 100% and from 8 to 83%, respectively. A negative effect of gold nanoparticles on the mortality was observed in adult insects infected by *S. feltiae* (Owinema). Despite this, in many cases, the addition of nanoparticles increased the efficiency of EPNs, used in the integrated pest control. Use of nanoparticles in agriculture, as antibacterial and antifungal agents, does not affect negatively EPNs pathogenicity under laboratory conditions. Instead of that addition of nano particles of Ag, Au or Cu may slightly increase the efficacy of nematodes but is necessary to do the field trials to verify the results (Kucharska et al. 2016).

In another study the silica nanoparticles were evaluated for the control of nematode—*Caenorhabditis elegans*. Degeneration of their reproductive organs was reported by the application of NPs (Pluskota et al. 2009). It was found that the exposure time and the concentration of the nanoparticles greatly influenced the mortality rate of invasive larvae of EPNs (Kucharska and Pezowicz 2009; Kucharska et al. 2011b). In *C. elegans* there are also reports of toxicity of nanoparticles such as titanium oxide, ZnO, Al_2O_3, silver, and Fe_2O_3 (Wang et al. 2009; Roh et al. 2009). Population of plant-parasitic nematodes on Bermuda grass was significantly reduced by application of nano silver particles and improved the turfgrass quality (Jo et al. 2013). Likewise, when the second-stage juveniles of *Meloidogyne incognita* when exposed to silver, silicon oxide, and titanium oxide nanoparticles under laboratory conditions; it was seen that all treatments of nano-Ag and 0.02% TiO_2 nanoparticles completely controlled *M. incognita* (Ardakani 2013).

8.5 Conclusions

Since the discovery of the abilities of fungi and nematodes as biological controllers of agricultural pests, great efforts have been made to achieve the efficient methods of application, among which are the creation of formulations capable of efficiently fulfilling their control purposes. One of the most recent approaches has been the combination of fungi and nematodes with nanoparticles, to increase the controlling power of these organisms. The combination with nanoparticles has been very useful to achieve a greater penetration effectiveness of the entomopathogenic fungi inside the insects that they parasitize, as well as to increase the mortality of the controlled pest insects. In contrast, less is known about the help that nanotechnology can provide in association with entomopathogenic nematodes. However, there is no doubt that with deeper future research, advances will be made both in the mechanisms that govern such interactions and in the breadth of their applications in this and other areas of modern agriculture.

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Chapter 9
Nanosensors for Plant Disease Diagnosis: Current Understanding and Future Perspectives

Prem Lal Kashyap, Sudheer Kumar, Poonam Jasrotia, D. P. Singh and Gyanendra Pratap Singh

Abstract Reliable and timely detection of plant pathogens plays an important role in crop health monitoring to reduce disease spread and facilitate effective management practices. Several methods have been employed for diagnosing crop diseases including visual inspection of symptoms, serological assays, and DNA-based detection of pathogen. These techniques are less reliable at asymptomatic stage. Additionally, they are time consuming, required costly equipment, produced false negative results from cross contamination, and need professional experts. Another most important limitation is their inability to reach at farmers field. To overcome these hurdles, recent developments in nanotools enabled to miniature the processes for developing biosensors for detecting pathogen presence in plants using antibody, DNA, and volatile compounds as biosensing receptors. Thus, nanobiosensor-based technology provides a new dimension in plant diseases diagnostic systems by offering nondestructive, minimally invasive, economical, and easy-to-use systems with enhanced detection limit, sensitivity, specificity, and on-site detection of plant pathogens. Briefly, the present chapter provides an overview in the development of nanosensing systems for plant pathogen diagnostics.

Keywords Agriculture · Detection · Diagnosis · Diseases · Electrochemical · Nanotechnology

9.1 Introduction

Plant pathogens decline global food grain production by 14% (Khiyami et al. 2014), and under favorable conditions some pathogens can cause complete crop failure (Ray et al. 2017). The occurrence in severity and spatiotemporal dispersal of diseases poses a paramount peril for safeguarding of global food production (Khater et al. 2017; Kashyap et al. 2017a; Savary et al. 2012; Mann et al. 2008; Oerke 2006).

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Moreover, combined influence of climate shift, globalization, elevated mobilization of people and pathogen, and rapid evolution of pathogen vectors, further enhance the expansion of sinister plant pathogens (Kashyap et al. 2018a; Bebber et al. 2014). For instance, rice blast pathogen variant, *Magnaporthe oryzae* pathotype *Triticum* was noticed on wheat in Northern part of Paraná (Brazil) in 1985 and expanded in many South American countries, now detected in Bangladesh in 2015 (Malaker et al. 2016). Similarly, the Ug99 race of black rust of wheat pathogen (*Puccinia graminis* f. sp. *tritici*) has evolved and migrated from Kenya and Ethiopia to other countries. Since 1999, the Ug99 race lineage has been reported from various parts of Africa and adjoining Middle East countries (Yu et al. 2017). According to estimates, Ug99 race is causing 10% yield losses in Asia that accounted to approximately 1–2 billion US dollars per annum (Duveiller et al. 2007). Another example is of *Tilletia indica* which poses a great challenge to the grain industry, owing not to direct yield loss but to quarantine restrictions that may impede the movement of affected wheat grain at global level (Kashyap et al. 2018b). Kashyap et al. (2016) mentioned that combined invasion of insect pests and diseases could cause 82 and 50% attainable yield losses in cotton and food grain crops, respectively. Similarly, Cerda et al. (2017) also reported that insect pests and diseases appeared on the foliage of perennial crop have the potential to cause 26 and 38% primary and secondary yield losses, respectively. Though diseases appear in agricultural fields are strategically tackled by fungicides and resistant crop cultivars, pathogen population rapidly mutate and adapt to these disease management tactics. Therefore, it is very imperative to develop sensitive, authentic, and quick detection assays for plant pathogens present at low concentrations and even in the hosts that act as symptomless carriers.

Current tools used to detect crop pathogens, includes visual inspection, isolations onto growth media, bioassays in which a sensitive indicator is inoculated and inspected for specific symptoms, microscopy, serology, and molecular techniques like polymerase chain reaction (PCR), DNA fingerprinting, quantitative real-time PCR (qPCR), isothermal amplification assays, reverse transcription-PCR (RT-PCR), nucleic acid blot assays, microarrays, and next generation sequencing (Kaur et al. 2019; Boonham et al. 2014; Kumar et al. 2013; Singh et al. 2014; Sharma et al. 2017; Rai et al. 2018). Several reviews addressed detection and diagnosis of crop pathogens by traditional and advanced nucleic acid-based techniques (Le and Vu 2017; Kashyap et al. 2017b; Martin et al. 2016; Martinelli et al. 2015; Nezhad 2014; De Boer and López 2012; Kashyap et al. 2011; Sankaran et al. 2010; Vincelli and Tisserat 2008; McCartney et al. 2003). The serological assays (immunodiffusion test, enzyme-linked immunosorbent assay, radio-immunosorbent assay, western blot analysis, dipstick immunoassay, dot immunobinding assay, tissue blot immunoassay, and serologically specific electron microscopy immunosorbent assays) and lateral flow devices (LF) have been described and developed to detect antigens of pathogen origin (Sharma et al. 2017; Martinelli et al. 2015; Souiri et al. 2014). Serological assays based on monoclonal antibodies offer high specificity and are widely used for on-site field level detection and diagnosis of pathogens from large number of cereals and horticultural crops (Miller et al. 2009; López et al. 2009). The ELISA sensitivity mainly relied on several factors which include type of pathogen (bacteria, fungus, virus, etc.), freshness of collected plant sample, and titer. For instance, minimum 100 cfu ml^{-1} of plant sample is required to detect and confirm the presence of bacteria (Boonham et al. 2014; Fegla and Kawanna 2013; Schaad et al. 2003). On the other hand, nucleic acid-based assays are more unswerving and specific to detect single target from a sample containing mixture of multiple pathogens. Therefore, these assays are well suited for simultaneous detection of several targets in a sample. PCR-based molecular assays offer several merits over serological assays. These include: (1) the capability to detect a single target in intricate mixtures, (2) quick and specific detection of multiple targets, and (3) the ability to detect uncultivable pathogens (bacteria, viruses, and phytoplasma) from environmental samples. In addition, cost of PCR-based analysis of individual sample is less than one euro (Martinelli et al. 2015). In PCR-driven diagnostics, strain or species-specific primers are developed from DNA regions of target pathogen and exploited for DNA amplification. Amplicons generated from target nucleic acid sequences are widely used as a DNA barcode to diagnose and identify different types of bacterial, fungal, and viral pathogens (Kashyap et al. 2017c). Though, the serological and nucleic acid-based detection are rapid and sensitive but unable to reach at farmer's field. Their efficiency largely depends on the precise and targeted designing of probes and oligonucleotides. Additionally, forged negative results can be occurred due to cross-contamination of chemical and reagents during PCR assay. Further, these reagents also cause slab amplification of target DNA, leading to the generation of spurious positive results by amplifying non-target DNA. Another drawback is related to the limited application of PCR-based diagnostics under field conditions (Schaad and Frederick 2002; Martinelli et al. 2015). To conquer such drawbacks, sensor-based innovations have been employed to develop portable tools for field diagnosis of plant pathogens (Khater et al. 2017; Fang and Ramasamy 2015). These sensors offer a wide range of paraphernalia for researchers interested in the identification, characterization, and monitoring of crop pathogens (Kashyap et al., 2016). Biosensors are categorized based on the bio-recognition principles and signal transduction mechanism (Table 9.1) and principally include thermal, optical, electrochemical, and piezoelectric sensors (Kwak et al. 2017; Ray et al. 2017; Martinelli et al. 2015). Emerging evidences indicated that nanobiosensors can be used in association with biomarkers for extracting rapid, precise, and accurate information related to early infection and progress of disease under filed conditions (Ray et al. 2017; Khater et al. 2017). Nanosensors can be grouped based on detection targets, their constituent materials, and the signals used by them to transmit information (Fig. 9.1). Recent reports clearly mentioned field application of nanosensors as an excellent tool to render crop cultivation more sustainable and safer by minimizing expensive use of agrochemicals employed for maintaining crop growth and health (Jasrotia et al. 2018). Table 9.2 provides a brief overview of different kinds of nanosensors designed so far for identification, characterization, and monitoring of field pathogens. This chapter highlights the important technological progress made in the field of diagnostics and quantification of crop pathogens, with special focus on nanobiosensors.

Table 9.1 Comparison of nanosensors developed for plant pathogens detection

Parameter	FRET	SERS	Electrochemical	Piezoelectric
Mechanism	Recognition element fused to a reporter element (fluorophore pair having overlapping emission spectra) and led to conformational change in the energy transfer between the fluorophores	Enhances Raman signals of analytes adsorbed on the surface of metal nanoparticles by up to 10^{14}	Contained a working electrode, counter electrode, and reference electrode. Based on the electrochemical response or electrical resistance change of materials caused by reaction with analytes	Converts mechanical vibration into an electric signal
Analyte	DNA, antibody	Adenine dinucleotide	DNA, antibody, Plant thiols	Mechanical forces
Sensitivity	High	Ultra-high (single molecule detection)	High (ppt–ppm range); Sensitive to temperature or pH	Real-time monitoring of the mechanical environment (plant growth)
Data analysis and interpretation	Tedious and difficult	Tedious	Simple and direct	No optical readout
Instrumentation	No	Yes	Yes (on-site power source for the sensor)	Yes
Cost	High	High	Low	High
Simplicity	No	No	Yes	Yes

9.2 Nanoparticles as Sensing Elements

Nanoparticles as a sensing element offer improved detection limit in diagnosing different kinds of bacterial, fungal, and viral diseases (Chartuprayoon et al. 2010; Yao et al. 2009; Boonham et al. 2008; Baac et al. 2006). Usually, nanoparticles alone or with combinations are employed in fabrication of diagnostic tools, which either detect pathogen directly or detect indicative compounds involved in advancing disease. Antibody-functionalized gold nanorods have been utilized for quick detection of viral infections imposed by *Odontoglossum ringspot virus* (*ORSV)* and *Cymbidium mosaic virus* (*CymMV)* in ornamental crops. The limit of detection (LOD) values for *ORSV* and *CymMV* infections in orchid leaves was found to be 48 and 42 pico gram ml^{-1},

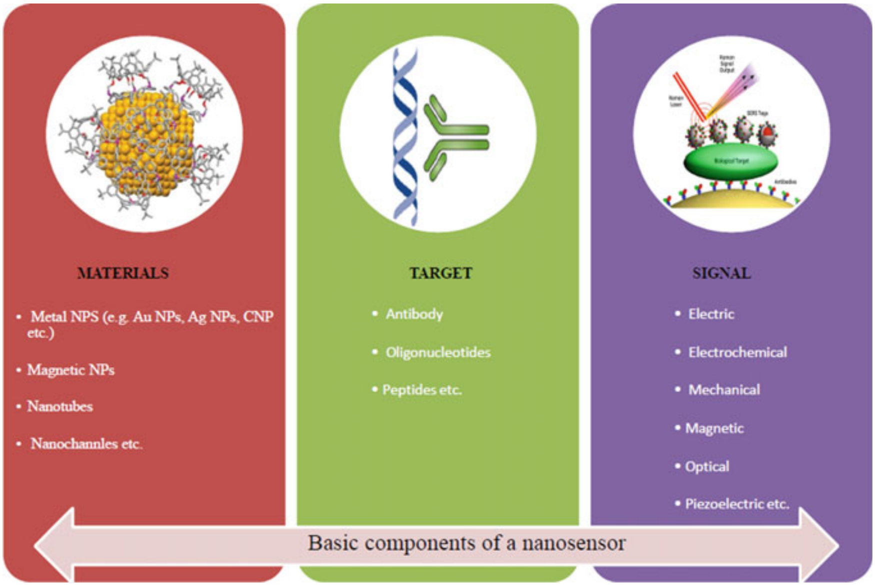

Fig. 9.1 Basic components of a nanosensor

respectively (Lin et al. 2014). Singh et al. (2010) devised gold nanoparticle-based immunosensor for the confirmation of Karnal bunt (*Tilletia indica*) infection in wheat using SPR technique. In addition to SPR, quartz crystal microbalance (QCM) technique was also reported for detecting the presence of viruses in plants. QCM technique was able to confirm the presence of *ORSV* and *CymMV* viruses up to the concentration of 1 ng in orchids (Eun et al. 2002). Yao et al. (2009) synthesized and applied fluorescence silica nanoparticle in combination with antigen specific to *Xanthomonas axonopodis* pv. *vesicatoria* to confirm bacterial spot disease in solanaceous crops. An electrochemical sensor containing modified gold electrode with copper (Cu) nanoparticles was devised by Wang et al. (2010) to detect the presence of *Sclerotinia sclerotiorum* fungus in oilseed crop. Their experimental findings indicated that gold electrodes modified with copper nanoparticles could be used as salicylic acid (SA) sensor, as Cu nanoparticles significantly improved the electrochemical behavior of SA. For the quantification of infection level of *Botrytis cinerea* in apple, grape, and pear fruits, Fernández-Baldo et al. (2010) fabricated a carbon-based screen-printed electrode using microfluidics principles. They employed competitive immunoassay technique and used to identify *B. cinerea* antigens by immobilizing on 3-aminopropyl-modified micro magnetic beads. The major merits of the developed assay are short assay time (40 min) and precise detection limit (0.008 μg ml^{-1}). Lithographically patterned nanowire electrodeposition (LPNE) technique using polypyrrole (PPy) nanoribbon modified chemiresistive sensor was employed by James (2013) to develop biosensor for confirming the presence of *Cucumber mosaic virus* (*CMV*) with a detection limit of 10 ng ml^{-1}.

Table 9.2 Some reported nanosensors based assays for diagnostics of plant pathogens

Sensor	Nanomaterial	Target pathogens	Target	Test host(s)	Type of study	Detection limit	Duration of assay	Sensitivity	References
Electrochemical	Colloidal AuNPs	*Pseudomonas syringae DC3000*	DNA	*Arabidopsis thaliana*	Laboratory	NM[a]	60 min	10^4 times more sensitive than PCR/gel electrophoresis	Lau et al. (2017)
Electrochemical	SnO_2 and TiO_2 NPs	*Phytophthora cactorum*	*p*-ethylguaiacol	Strawberry	Laboratory	35–62 nM	NM	High	Fang et al. (2014)
Fluorometric	Tioglicolicacid capped cadmium-telluride quantum dots (QDs) and CNPs	*Citrus tristeza virus*	Antibody	*Citrus*	Laboratory and field conditions	220 ng mL^{-1}	NM	Highly sensitive than ELISA	Shojaei et al. (2016)
FRET	Tioglicolicacid-modified Cadmium-Telluride QDs (CdTe-QDs)	*Polymyxa betae*	Antibody (Anti glutathione-S-transferase protein)	*Beta vulgaris* and *Hordeum vulgare*	Laboratory	0.5 µg mL^{-1}	NM	NM	Safarpour et al. (2012)
FRET	CdSe QDs	*Ganoderma boninense*	DNA	Oil palm	Laboratory	1.12×10^{-12} M	NM	1 nM	Bakhori et al. (2012)
FRET	CdSe QDs	*Ganoderma boninense*	DNA	Oil palm	Laboratory	3.55×10^{-9} M	20 min	NM	Bakhori et al. (2013)
FRET	Tioglicolic acid-modified cadmium-telluride quantum dots (CdTe-QDs)	*Candidatus Phytoplasma aurantifolia* (Ca. P. aurantifolia)	Antibody (IMP)	Lime	Laboratory and field	5 ca. P. aurantifolia/µ l^{-1}	NM	High	Rad et al. (2012)

(continued)

Table 9.2 (continued)

Sensor	Nanomaterial	Target pathogens	Target	Test host(s)	Type of study	Detection limit	Duration of assay	Sensitivity	References
Piezoelectric	Gold NP-coated QCM crystals	*Maize chlorotic mottle virus*	Antibody (anti-MCMV)	Maize	Laboratory	250 ng mL^{-1}	NM	Highly sensitive than ELISA	Huang et al. (2014)
Piezoelectric	QCM crystals	*Cymbidium mosaic potexvirus (CymMV)* and *odontoglossum ringspot tobamovirus (ORSV)*	DNA	Orchid	Laboratory	1 ng	NM	Highly sensitive than ELISA	Eun et al. (2002)
SERS	Nanotages composed of AuNPs core	*Botrytis cinerea*, *Pseudomonas syringae*, and *F. oxysporum* f. sp. *conglutinans, F. oxysporum* f. sp. *lycopersici*	DNA	*Arabidopsis thaliana* and tomato	Laboratory and field conditions	2.5 ng	40 min	10^4 times more sensitive than PCR/gel electrophoresis	Lau et al. (2016)
SERS	Ag NPs	*Phytophthora ramorum*	DNA	*Rhododendron*	Laboratory and field conditions	NM	NM	NM	Yuksel et al. (2015)

[a] NM = Not mentioned

Etefagh et al. (2013) designed senor based on nanoparticles and nanolayer of copper oxide (CuO) for detecting *Aspergillus niger* in food. They used sol–gel and spray pyrolysis techniques for developing CuO nanoparticles and nanolayers and used electrical resistance principle for measuring the biosensing properties of developed nanostructure. Zhang et al. (2013) utilized the concept of combining upconversion nanoparticles (UCNPs) as biolabeling with immunomagnetic separation for rapid and precise detection of plant viruses. They coated magnetic nanoparticles (MNP) of 100 nm size with different antibodies and employed them as signal probes to capture *Tomato ringspot virus* (*ToRSV*), *Bean pod mottle virus* (*BPMV*), and *Arabis mosaic virus* (*ArMV*). The major merits of this assay include the simultaneous detection of several independent organic fluorophores, elimination of nonspecific absorption of viruses, low fluorescent background and high sensitivity, and selectivity to trace target viruses. Besides this, the developed assay is easy to perform and able to diagnose the infected plant samples in short span of 2.5 h. Similarly, the application of MNPs in designing user-friendly magnetic immunoassay for the quantification of *Grapevine fan leaf virus* (*GFLV*) was demonstrated by Rettcher et al. (2015). In this assay, immobilization of monoclonal antibodies recognizing the *GFLV* capsid protein was made onto immunofiltration columns and further used to link MNPs. Immunofiltration with magnetic labeling in a double-antibody sandwich configuration was adopted to quantify *GFLV* concentration in leaf sap. Mechanistically, a magnetic frequency mixing technique was employed, where a two-frequency magnetic excitation field was applied to generate a frequency signal in the resonant detection coil that corresponds to the virus concentration present in the immune-filtration columns. In comparison to ELISA assay, the major merit of developed assay was 17-folds more quantification sensitivity and minimum assay time (28 min). Moreover, the LOD of assay was 6 ng ml^{-1}. Besides this, synthesis and application of nanoparticles derived from semi-conductive metal oxide have been described for volatile organic compounds (VOC) detection. For instance, Fang et al. (2014) have established the utility of SnO_2 and TiO_2 nanoparticles for the detection of *p*-ethylguaiacol chemical released by strawberry fungus, *Phytophthora cactorum*. Besides the application of nanoparticles in the detection of disease marking VOC, their potential application in detecting compounds of pathogen origin has also been reported (Fang and Ramasamy 2015).

9.3 Types of Nanosensors

9.3.1 Fluorescence Resonance Energy Transfer (FRET) Nanosensor

FRET nanosensor represents a type of optical sensor which operates on the principle of transfer of fluorescence resonance energy and its measurement (Algar and Krull 2008). Theoretically, FRET employs two different kinds of fluorescent dyes termed as a donor (for transferring energy after excitation by a light source) and an acceptor (absorb excited energy) via intermolecular dipole–dipole interactions (Stanisavljevic et al. 2015). The energy transfer occurs when the emission spectrum of the donor dye overlaps the excitation spectrum of acceptor dye. This happened when the distance between two dyes lies in the range of 1–10 nm (Grecco and Verveer 2011). Besides this, a substrate-specific binding domain, generally flanked by a suitable donor and acceptor dye at distinct terminals, is used for successful FRET pairing (Ellinger and Voigt 2014). Because of substrate binding, a change in distance or orientation of the two fluorophores occurs that further quantified as a measurable change in the form of energy transfer (Kwak et al. 2017).

9.3.2 Surface-Enhanced Raman Scattering (SERS) Nanosensor

SERS is a unique type of a spectroscopy detection tool that can detect analytes at individual molecule level. Generally, this type of nanosensor is composed of metal nanoparticles surfaces that improve Raman scattering pattern features of the adsorbed molecule via laser excitation (Kahraman et al. 2017). Raman signals of molecules adsorbed on the metal nanoparticles coated surface can be enhanced by a factor of up to 10^{14} that is comparable to or even higher than fluorescent organic dye (Stiles et al. 2008). Two different mechanisms responsible for triggering SERS effects include electromagnetic effect and chemical effect (Sun et al. 2008). Electromagnetic effect in SERS nanosensor is used to enhance the electromagnetic field near the nanoparticle surface. Interestingly, this long-range enhancement in electromagnetic effect occurs at wider distance away from the nanoparticle surface (10–200 nm). On the other hand, chemical effect reflects short-range transfer of charge between the guest molecule and nanoparticle. This shorter-range chemical effect occurs only when absorption of an analyte takes place on a surface coated with nanoparticles (Wei et al. 2015). For this purpose, Au and Ag nanoparticles are generally used due to their strong and tunable plasmon resonance in the near-infrared (NIR) region. By taking advantage of SERS, several sensors have been developed for pathogen detection in agriculture field (Chen and Park 2016).

9.3.3 Electrochemical Nanosensors (ECN)

Electrochemical nanosensor (ECN) is an innovative and potent technique to detect crop pathogens at an early stage due to its simplicity, low cost, high sensitivity, ease of miniaturization, and capability for direct data analysis. ECN provides an excellent way to examine any biological sample owing to its capability of direct translation of a biological event to an electronic signal (Zhu et al. 2015).

Typically, electrochemical nanosensors composed of three different types of electrodes defined as counter electrode, reference electrode, and working electrode (Barry and O'Riordan 2015). For measuring conversion of any biological event or chemical signal into an electrical signal, various instruments viz., amperometry, potentiometry, voltammetry, and conductometry have been employed (Qureshi et al. 2009). Electrochemical electrodes designed with nanomaterials have the advantage of a high active surface area that allows higher sensitivity and a broader range of concentration detection of plant-related redox and ion species (Clausmeyer and Schuhmann 2016). Due to these advantages, ECN can be applied to pathogen detection in the field and horticultural crops (Srivastava et al. 2018).

9.3.4 Piezoelectric Nanosensor (PZN)

Piezoelectric nanosensor (PZN) has the capability to translate mechanical energy, ultrasonic vibrations, and biofluid hydraulic energy of any biological event into electric energy and, therefore, providing new avenues for real-time monitoring of pathogenic infection in plant systems. Principally, piezoelectric sensors work on the concept of monitoring and determination of change in mass due to biomolecular interaction between antibody and its respective antigenic determinant (Byrne et al. 2009). For instance, shift in resonance frequency of quartz crystal due to mass change has been measured by calculating change in frequency of the QCM.

9.4 Potential Applications of Nanosensors in Plant Disease Diagnosis

Nanobiosensor-based technology provided a new dimension in plant diseases diagnostic systems (Table 9.2) by offering economical, user-friendly, nondestructive, and minimally invasive system with enhanced sensitivity, specificity, and detection limit for on-the-spot detection of crop pathogens. As mentioned earlier, the sensor was developed by Eun et al. (2002) for *CymMV* and *ORSV* detections by coating virus-specific antibodies on QCM surface. For binding of virions, they immobilized antibodies specific to test viruses present in infected sample of orchid plants. They observed that the mass changes at the QCM surface is negatively associated with the frequency of resonance oscillation. Later, QCM-based biosensor has been designed by Huang et al. (2014) for rapid diagnosis of *Maize chlorotic mottle virus* (*MCMV*) in corn. Gold surfaces of QCM crystals was coated with a mixture of 10:1 3-mercaptopropanoic acid and 11-mercaptoundecanoic acid to create a self-assembled monolayer, and antibodies specific to *MCMV* was cross-linked on the surface for precise and accurate detection of virus inoculum. Moreover, LOD was found to be 250 ng ml^{-1}. The improvements in the level of sensitivity, selectivity, and reproducibility of designed biosensor for *MCMV* advocate that the piezoelectricity-driven QCM sensor could be a better choice for rapid, precise, and reliable diagnostics at field level.

Safarpour et al. (2012) demonstrated the utility of fluorescent nanoparticles for designing a diagnostic system for sensing *Polymyxa betae*. In their experiment, they biofunctionalized quantum dots (QDs) with a monoclonal antibody showing specificity toward *P. betae*. Antibody corresponding to glutathione-S-transferase protein was dipped in an aqueous solution of Tioglicolicacid-modified Cadmium-Telluride QDs using electrostatic interaction principle. Antigen–antibody interaction was carried out by linking rhodamine dye with glutathione-S-transferase protein to form donor–acceptor complex. As a result of mutual kinship of antigen and antibody, resonance dipole–dipole coupling occurred and initiated fluorescence resonance energy transfer. It is noteworthy here that this nanobiosensor assay requires only 20 µl of biosample and hence could be useful in critical situations where sample is limited and less in quantity. The LOD for this assay was found to be ≥ 0.5 µg ml^{-1}, which was much better than that of the conventional ELISA (2 µg ml^{-1}) and illustrated precise sensitivity, specificity, and 100% reproducibility (Safarpour et al. 2012). Further, Bakhori et al. (2012) developed a DNA biosensor based on FRET utilizing quantum dot (QD) for early detection of basal stem rot disease of oil palm caused by *Ganoderma boninense*. They employed modified CdSe/ZnS QD to conjugate single-stranded DNA of *G. boninense*. Further, DNA of *G. boninense* was sandwiched with conjugated QD-ssDNA, and labeling of reporter probe was achieved with Cy5 dye. As a result of hybridization, sandwich hybrid allowed detection of related gene sequences of *G. boninense* by generating FRET signals. It is essential to mention here that the designed DNA-based nanobiosensor is precise and sensitive enough to detect *G. boninense* with LOD value of 1.12×10^{-12} M. Similarly, QD-based nanobiosensor was also devised by Rad et al. (2012) for rapid and precise detection of Candidatus *Phytoplasma aurantifolia* associated with lime trees. In this diagnostic platform, immunodominant membrane protein derived from phytoplasma surface was used as a target protein to synthesize specific binding antibody. The synthesized antibody was further conjugated to tioglicolic acid-modified cadmium-telluride quantum dots prepared in an aqueous solution via electrostatic interaction. Antigen–antibody interaction was carried out by linking rhodamine dye molecule with immunodominant membrane protein to form donor–acceptor (QDs-Ab-IMPRhodamine) complex. As an outcome of strong mutual antigen–antibody interaction, resonance dipole–dipole coupling occurred and triggered fluorescence resonance energy transfer. Overall, the developed immunosensor displayed precise sensitivity, 100% specificity and LOD of 5 ca. *P. aurantifolia* μl^{-1} with acceptable stability.

In continuation of the above-mentioned reports, it is worth mentioning here that carbon nanoparticles (CNP) and their interesting features have classified them as excellent material for the development of fluorometry-driven nanosensors (Zuo et al. 2015). Recently, a fluorometric-based nanosensor for *Citrus tristeza virus* (CTV) using CNP has been reported by Shojaei et al. (2016).

They conjugated cadmium-telluride quantum dots with an antibody raised against *CTV*. Further, immobilization of coat protein of test virus on to the surface of CNP was performed to form immuno-complex for successful quenching interaction between the donor and the acceptor. It was observed that in the presence of the target proteins in the plant samples, CNP-tagged coat protein was competitively dislocated by free coat proteins and leading to fluorescence generation along with recovery of QD. The reported fluorometry nanosensor was found highly sensitive and specific than ELISA. The LOD was estimated to be 220 ng ml^{-1} of *CTV* (Shojaei et al. 2016). Based on the above-mentioned research findings, it can be concluded that FRET in association with quantum dots possessing unique properties that facilitate designing and development of new and better quality sensors for field application.

Yuksel et al. (2015) devised label-free and species-specific diagnostic system for *Phytophthora ramorum*. They accomplished nucleic acid-based detection of *P. ramorum* by amplifying GTP-binding protein (*Ypt1*) region of *P. ramorum* by LATE-PCR followed by hybridization between immobilized capture probes and *Ypt1* gene sequence of pathogen origin. Based on their experimental findings, they concluded that SERS-based nanosensor has the potential to capture adenine containing target DNA from infected *Rhododendron* leaves and can work along with adenine-free capture probes. Further, to demonstrate the feasibility of developed assay under field conditions, a novel isothermal amplification technique has been employed. The results indicated that SERS-based nanosensor largely dependent on DNA–DNA hybrid formation and could be performed in a portable handheld Raman device that allows rapid and on-the-spot detection of pathogen under field conditions. Working on similar lines, Lau et al. (2016) used SERS-labeled nanotags and recombinase polymerase amplification (RPA) principles to develop a brisk, specific, and sensitive point of care tool to detect multiple pathogens (*Botrytis cinerea*, *Pseudomonas syringae,* and *Fusarium oxysporum*) causing infection in *Arabidopsis thaliana* and tomato. The developed nanosensor was found more sensitive than conventional PCR and could able to detect as low little as two copies of pathogenic DNA.

Fang et al. (2014) explored the detection capabilities of TiO_2 and SnO_2 NP for the designing of electrochemical sensor to detect *Phytophthora cactorum* infection in strawberry fruits. Screen-printed carbon electrodes modified with nanoparticle (SnO_2 and TiO_2) was used to perform electrochemical detection of volatile compound (*p*-ethylguaiacol) produced by fungus in infected strawberry fruits. The experimental findings showed that electrode coated with metal oxide nanoparticles possesses greater sensitivity, and LOD was found to be 35–62 nM *p*-ethylguaiacol. Moreover, other plant volatiles do not interfere with the amperometric recognition of *p*-ethylguaiacol signal (Fang et al. 2014). Additionally, the study revealed that metal oxide nanoparticles provide reasonable and economical alternative to costly electrode material like gold and platinum employed in the designing of amperometric sensor. Recently, Lau et al. (2017) also developed an electrochemical nanosensor to diagnose infection of *P. syringae* in plant samples before symptom expression. The developed sensor worked on the principle of isothermal nucleic acid amplification of target pathogen by recombinase polymerase followed by measurement of gold nanoparticle-mediated electrochemical signal by differential pulse voltammeter instrument. The inventors confirmed that the 60-min assay is 10^4 folds more sensitive than traditional PCR-driven diagnostic assays.

9.5 Conclusions and Future Directions

This chapter has described the promising role of nanosensors and their probable applications in plant disease diagnosis. Nanosensors entail binding or reaction with target species or strains and eventual transformation into detectable signals, thereby facilitating quick, precise, and early diagnosis of disease inciting agents to ensure quality food production. Additionally, they offer benefits of specificity, sensitivity, portability user-friendly detection of crop pathogen under field conditions. However, some constraints relating to interfering substances, non-specific binding, aggregation, and toxicity of NPs in planting materials should be addressed to realize their full potential and implementation as nanosensors in agriculture and allied sectors. The authors concluded that basic research is still required to improvising the present-day sensor technology, sensing stratagems and refining of analytical instrumentations and protocols for crop disease diagnosis at an early stage.

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Chapter 10
Use Nanotools for Weed Control and Exploration of Weed Plants in Nanotechnology

Mohamed A. Balah and Ramesh Namdeo Pudake

Abstract During the last decades, agriculture sector faces many difficulties due to worldwide loss by pests estimated by 30% from food production. Within this, weed caused about 13% loss, besides the ill effects of synthetic herbicides on human and the environmental health. The present chapter reviews the use of nanotools in weed management, in which many trials are being conducted to facilitate this technology for future weed management, by minimizing the costs and the environmental effects of the use of chemical herbicides. Nanoherbicides provide a good opportunity for farmers to control annual, perennial, and parasitic weeds by blending with the soil or sprayed on weed plants without the use of excessive amounts chemicals to leaving any toxic residues and environmental problems. Nanoformulations are being used in weed control, especially polymer formulation (control release or nanocapsulation) or nano-emulsions for natural product extracts, essential oils, and active ingredient (AI) of synthetic herbicides. Conventional application of herbicide is causing serious hazard for human health through water pollution. The use of nanoparticle for degradation of polluting herbicides from water sources' aspect is also covered in this chapter. Biological synthesis is an efficient method for nanoparticles and has been used in various applications. Many researchers are focusing on using weed to find an environment-friendly technique for producing well-characterized nanoparticles which has been reviewed in this chapter.

Keywords Nanotechnology · Nanoherbicides · Nanoformulation · Weed management · Photodegradation · Biological synthesis

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10.1 Introduction

Weeds are uncultivated plants that grow associated with crops in agricultural lands and other places. They are not desirable because they cause various economic and environmental losses. It reduces the crop productivity, causes loss of groundwater by consumption and evaporation, acts as obstacle in the flow of water canals and as barrier for navigation in the airports and railways, and reduces the quality of land, especially the presence of perennial species. In general, weeds are difficult to eradicate and control for many reasons. Seeds are produced in large numbers that are not comparable to crops. They have more than one means of propagation and have a long period of dormancy to ensure the length of survival. Many of which are like the crop plants that are associated with them, especially in the early stages of development, which saves them from disposal, and ends their life period quickly and before the maturity of crops. The worldwide plant disease caused 13%, insect 14%, and weed 13% loss in food production and accounted 2000 billion $ economic loss per year (Pimentel 2009). The weed control methods can be divided into three large sections, including mechanical, biological, and chemical control. The widespread use of herbicides causes environmental pollution and many problems. Some are like the high cost of synthetic herbicides, concern for the environmental damage, the public concern for food safety, the unacceptability of many herbicides chemical groups, the lack of new herbicide with new modes of action, the reduction in the number of registered herbicides, and the rapid evolution of herbicide resistant weeds.

In recent two decades, many advanced technologies are being introduced in the field of weed control to make the process easier and more efficient. Among the latest technological advancements, nanotechnology occupies a central position. It has many applications in all stages of production, processing, storing, packaging, and transport of agricultural products. The reduced use of herbicides and pesticides with increased efficiency, controlled release, and targeted delivery will lead to precision farming. Preliminary studies show the potential of nanomaterials in improving seed germination and growth, plant protection, pathogen detection, and pesticide/herbicide residue detection (Khot et al. 2012). This chapter reviews the use of nanotools that has proved highly successful in control of different types of weeds and in many sites and weed communities. Recent research producing crystals in the nano-size range has provided evidence of improved efficacy of agrochemicals (Crooks et al. 2003). Worldwide consumption of herbicides represents 47.5% of the 2 million tons of pesticide consumed each year. However, the heavy use of herbicides has given rise to serious environmental and public health problems. It is therefore important to develop new herbicide formulations that are highly effective, that are safer (for the worker and for the environment), and that involve a low cost/production ratio. In this sense, controlled release formulations of herbicides have become necessary in recent years, since they often increase herbicide efficacy at reduced doses (Sopeña Vázquez et al. 2009). The present chapter also reviews in detail the components of various types of herbicide formulations, with an emphasis on controlled release formulations and micro-encapsulation. These kinds of release systems could reduce the herbicide resistance potential, maintain the activity of the active ingredient, and prolong their release over a longer period (Manjunatha et al. 2016).

Nanoherbicides represent an efficient means specially in the early weed control and are being developed to address the problems in perennial weed management and exhausting weed seed bank. Research in nanotools has led to the emergence of unconventional forms of herbicides that have their unique characteristics than those used for decades. Along with the new area of research is emerging where worthless weeds are being used to synthesize different nanoparticles for various applications. Also, to address the issue of herbicides polluting the water and soil has encouraged many studies on the use of nanoparticles for degradation of herbicides. Despite all these scientific attempts, nanotechnology in the field of weed control, herbicide degradation and biosynthesis of nanomaterial face many futuristic difficulties. This chapter reviews the current status of nanotechnology in weed management and its related aspects.

10.2 Types of Different Weeds

The life cycle of broadleaf annual weeds gets completed by one winter or summer season. The seeds of these weeds germinate in the fall, their vegetative growth occurs in the winter, and their fruit growth gets completed before entering summer. The few examples of major broadleaf annual weeds are *Medicago polymorpha*, *Melilotus indicus*, *Anagallis arvensis*, *Beta vulgaris*, *Brassica kaber*, *Capsella bursa-pastoris*, *Chenopodium* sp., *Malva parviflora*, *Rumex dentatus*, *Urtica urens*, *Sonchus oleraceus*, *Euphorbia* sp., *Coronopus* sp., *Emex spinosus*, *Vicia sativa*, *Cichorium endivia*, *Senecio glaucus*, *Calendula arvensis*, *and Lathyrus hirsutus*.

Annual narrow-leaved weeds germinate in the spring, and their vegetative growth occurs in the summer and matures before entering the winter. The narrow-leaved winter weeds include *Avena* spp., *Phalaris* sp., *Lolium temulentum*, *and Polypogon monspeliensis*, while the narrow-leaved annual summer weeds include *Echinochloa crus-galli*, *Digitaria sanguinalis*, *Echinochloa colonum*, *Eleusine indica*, *Dactyloctenium aegyptium*, *Cenchrus ciliaris*, *Brachiaria eruciformis*, *Setaria viridis*, *and Cyperus difformis*. The important risks of annual weeds are clearly shown in its huge seed production, and the fight against these weeds requires a huge effort by farmer. The use of nanotechnology for weed control can help the farmers for efficient control of the weed.

Perennial weeds are those weeds that stay in the soil more than 3 years. Generally, they are difficult to control, as they reproduce by more than one way like they may multiply with seed or rhizomes or tubules or tubers or creeping roots. There are two major classes of perennial weeds. One is narrow-leaved weeds, including: *Imperata cylindrica*, *Cyperus* spp., *Cynodon dactylon*, *Phragmites* spp., *Alhagi* spp., *and Cyperus* spp. The second type is perennial broad-leaved weed that includes *Convolvulus arvensis*, *Arundo donax,* and *Conyza discoroidis*. Perennial weeds represent a direct threat to the optimal production of crops.

Parasitic weeds depend on the host crop to obtain food, through the roots or stem of the host plant. The examples are Cuscuta sp., *Orobanche crenata*, *Orobanche* aegyptiaca, *Orobanche minor,* and so on.

10.3 Nanoherbicides

Nanoherbicides are being developed to address the problems of all kind of weeds (Manjunatha et al. 2016), as nanotechnology can be used to improve the performance of many existing herbicides or to formulate an alternatives tool that is a quick, efficient, and economical means and exceeds the original product. Nanoherbicides as a "smart delivery system" provides an eco-friendly approach through reducing herbicide inputs, as well as providing control over where and when an active ingredient is released (Pérez-de-Luque and Rubiales 2009). But the manufacturing of nanometric herbicides is in its primary stages and is expected to make significant progress for increasing efficiency against weeds and reducing the quantities of herbicides used to reduce the effects on the environment. Some of the formulation and tools to achieve these objectives are discussed here in details.

10.3.1 Use of Polymer Nanoparticles

Pesticide formulation that increases the use efficiency and reduces environmental pollution is the need of present time. Due to their potential in changing the pesticide release profile, the polymeric nanoparticles have gained focus in the recent days. Encapsulation of herbicide in polymeric nanoparticles is being explored to achieve the environmental safety (Kumar et al. 2015b). In one study, the chitosan was used to encapsulate silver nanoparticles and paraquat herbicide. This nanoformulation was evaluated for controlled release and improved herbicidal activity against *Eichhornia crassipes*. Encapsulation efficacy was found to be 89.0%; controlled release study showed 90.0% of release of AI occurred at 24 h, and the distinct improved herbicidal activity was observed against *Eichhornia crassipes* by the formation of necrotic lesions in all the tested concentration of nanoformulation. Non-target effect study on the various soil parameters revealed that nanoformulation did not affect the soil macro- and micronutrients, soil enzyme, and soil microflora. Seedling emergence and plant growth parameters of the tested plant were not affected in the nanoformulation treatment (Namasivayam and Aruna 2014).

In another study, the researcher has reported the method for synthesis of poly (lactic-*co*-glycolic-acid) (PLGA) nanoformulation loaded with atrazine (Schnoor et al. 2018). An average size of nanoformulation was about 110 ± 10 nm before the lyophilization, and studies with potato plants had shown that 50% encapsulated herbicide was released in 72 h. The formulation resulted in reduced growth of potato plant and proved that PLGA nanoherbicides can be used as an alternative method for inhibiting weed growth (Schnoor et al. 2018). In one study, poly (l-lactide-*co*-glycolide)–poly(ethylene glycol)–poly(l-lactide-*co*-glycolide) (PLGA–PEG–PLGA) terpolymer with PEG (16%) was used as a biodegradable carrier for the controlled release of metazachlor and pendimethalin (Rychter et al. 2019). The addition of PEG helped in uniform progress of degradation, and thus a relatively constant release of herbicides was achieved. PEG–PLGA was also used for developing the delivery system for metolachlor (Tong et al. 2017). As the resultant formulation did not contain any organic solvent or surfactant, it reduced the chances of pollution. The water solubility of this hydrophobic weedicide was also enhanced. The bioassay and other analytical studies have revealed that the nanoformulation had increased the absorption in plants, but reduced cytotoxicity in preosteoblast cell line (Tong et al. 2017).

Nanocapsules of poly(ε-caprolactone) with three triazine herbicides (ametryn, atrazine, and simazine) had shown better stability and were less genotoxic than the free herbicides (Grillo et al. 2012). Similar results were obtained when the herbicidal activity of atrazine that was encapsulated in poly(ε-caprolactone) was evaluated using mustard (*Brassica juncea*). The results have shown that nanocapsules with 1/10th dose of atrazine dosage tenfold was similarly effective as compared to the commercial formulation (Oliveira et al. 2015). In another study with atrazine, poly(epsilon-caprolactone) nanoparticles were evaluated for its herbicidal activity and genotoxicity (Pereira et al. 2014). The nanoformulation was stable up to 3 months and was specific to target. The experiments confirmed the reduced mobility of herbicide in soil and lesser genotoxicity.

When chitosan and sodium tripolyphosphate (TPP) were used for making the nanoformulation of paraquat, similar results were obtained. To check the herbicidal activity, the maize and mustard plants were used as a model, and the absorption of herbicide in soil was also measured. Along with this, the cyto- and genotoxicity of was evaluated by cell culture viability assays and chromosome aberration test. The encapsulation efficiency was $62.6 \pm 0.7\%$ that reduced diffusion rate and ultimately the absorption by soil. Cytotoxicity and genotoxicity studies confirmed the less toxicity of nano-encapsulated herbicide as compared to the control. Herbicidal activity was also preserved, and the encapsulation was shown similar results as shown by pure AI (Grillo et al. 2014). In continuation to this study, the same group evaluated the fate of encapsulated herbicide in the environment. They studied the colloidal stability and toxicity of encapsulated paraquat in aquatic humic substances and found no significant changes in the physical–chemical stability of the nanoparticles. However, these humic substances help in reduction of the ecotoxicity and genotoxicity of nanoparticles containing paraquat. These kinds of studies are required in other formulations also, as it will help in better understanding of interaction between the carrier systems and the ecosystem (Grillo et al. 2015). In one study, when diuron was encapsulated in carboxymethyl chitosan nanoparticles, the herbicidal activity was only for target species (*Echinochloa crus-galli*) and not for non-target species (*Zea mays*) (Yu et al. 2015).

When alginate/chitosan and chitosan/tripolyphosphate nanoparticles was used to encapsulate the imazapic, imazapyr, and paraquat herbicides, the encapsulation had shown better performance in their mode of action, toxicity to other organism (dos Santos Silva et al. 2011; Maruyama et al. 2016). The poly(hydroxybutyrate-*co*-hydroxyvalerate) (PHBV) microspheres were formulated by emulsification/solvent evaporation method with atrazine herbicide, and 25% encapsulation efficiency was achieved. The release kinetics was altered to reduce the environmental loss (Lobo et al. 2011). All these results discussed above along with the other studies (Chi et al. 2017; Guo et al. 2014; Singh et al. 2015a) have shown that polymeric nanoparticles could serve as an herbicide carrier with lower environmental impact, comparable effect, and effective delivery.

10.3.2 Nano-emulsion

Nano-emulsion of herbicides could be another alternative for effective delivery of active ingredients. Nano-emulsion can be defined as a non-equilibrium colloidal system that contains oil(s)/surfactant(s)/water with particle size of diameter typically in the region of 20–200 nm. The nano-emulsion is generally optically translucent and sometimes transparent that is kinetically stable. It is being used in various drug and cosmetic formulations and food industry. Some of nano-emulsion formulations of herbicides are discussed below.

In one study, nano-emulsion formulations were produced from micro-emulsion-based pre-formulations of water-soluble herbicide glyphosate isopropylamine. It was generated with the low-energy emulsification of gentle stirring with 41% glyphosate. The nano-emulsion system had small particle size and lower surface tension and shown better results than the commercial formulation (Jiang et al. 2012). In another study, the nano-emulsion formulations with glyphosate displayed a significantly lower spray deposition on weeds studied as compared to commercial formulation—Roundup®. Still the visible injury rates of weeds treated with the nano-emulsion formulations were statistically equivalent to those relating to Roundup® at 14 days after treatment and were attributed to the enhanced bioactivity of the nano-emulsion formulations (Lim et al. 2013). These initial findings could aid the development of sustainable nano-emulsion systems as a greener alternative to advanced agrochemical formulations.

The essential oils from plants are being widely used in agriculture and food industries for their different role. Some essential oils have herbicidal properties. In past, there are studies carried out to fabricate and apply the nano-emulsion of plant essential oil for weed control. In our past study, we have used the formulation of *Thymus capitatus* L. (wild and cultivated thyme) and *Majorana hortensis* L. (marjoram) oils for control of *Convolvulus arvensis* and *Setaria viridis* (El Azim and Balah 2016). The results of this study have revealed that the prepared emulsion of *M. hortensis* was better as compared to the *T. capitatus*. Nano-E showed inhibitory effect on *C. arvensis* even at 5–7 leaves stage. In another study, the oil/water

(O/W) nano-emulsion NE of (*Satureja hortensis*) essential oil has shown the herbicidal properties. It affected the weed killing by interfering with its germination, growth, and physiological processes. The nano-emulsion was stable after 30 days of storage and indicated that it can be a promising natural herbicide for weed control (Hazrati et al. 2017).

10.3.3 Nano-absorbents

The application of herbicides that are adsorbed on carrier material can reduce the risk of groundwater contamination resulting from rapid leaching. Like other pesticides, this will limit the amount of herbicide immediately available for undesirable losses. Due to the cost and sustainability, the natural materials like clay and organic waste are of special interest as carrier material. Clay is very popular material for designing the slow release formulation of pesticides, as we can modify the surface by the adsorption of organic cations and transforming it from hydrophilic to hydrophobic. This modified clay mineral surface can adsorb organic active ingredients that have low solubility in water. This has been utilized to make slow release formulation of alachlor and metolachlor that showed improved weed control (El-Nahhal et al. 2000; Nir et al. 2000). Atrazine is a common herbicide that is effective for control of broadleaf weeds and is non-biodegradable in nature. Allophanic clays and nanoclay was added to modify the polymeric matrix containing atrazine, and a controlled release formulations (CRFs) were formulated (Cea et al. 2010). The formulation has shown a reduced leaching loss, and more seedling death was observed with nanoclay containing matrix (Cea et al. 2010). In another study, hydroxyapatite (HAp) was used as nano-adsorbent for atrazine. The formulation has efficiently controlled the growth of *Brassica* sp., and the results are attributed to the adsorbing ATZ over the surface of HAp NPs that restricted its premature runoff (Sharma et al. 2019).

The adsorption potential and applicability of surfactant-modified clinoptilolite (SMC) and montmorillonite (SMM) nanoparticles was evaluated with 2,4-D. This slow release formulation has showed the three times higher adsorption potential than the unmodified silicates (Bhardwaj et al. 2015). In one study, the 2,4-D was adsorbed on nanosized husk. The waste husk was considered as better alternative carrier for herbicide due to its easy availability. The optimum ration of nano-rice husk to 2,4-D was 1:0.1, and the mechanism of absorption was accounted to monolayer mode of sorption following chemisorption process. Due to the property of this formulation, it exhibited better herbicidal activity against Brassica plant (Chidambaram 2016).

In one study, the researcher used anionic clay and a commercial cationic organoclay as nanocarriers for imazamox (Imz) herbicide and found that it was adsorbed in interlayer structure. With the similar efficacy, the herbicide concentration in soil column was decreased by 20–35% as compared to commercial formulation (Khatem et al. 2019). The nanotubes of aluminosilicate clay mineral-Halloysite were loaded with botanical herbicide, and loading efficiency of 7.26 wt% eupatorium adenophora spreng (AIEAS) was achieved (Zeng et al. 2019). To slower down the release further, they incorporated this carrier in poly (vinyl alcohol)/starch composites (PVA/ST) film and found the significantly increased service life of bioherbicide.

All the results have indicated that the fabrication of effective nano-adsorbent for slow release of herbicides has great potential to reduce the agricultural runoffs and ensure their effective functioning. The adsorbing efficiency can be varying and mainly depends on method of synthesis and properties of nanocarriers. But the suitability of these nanoformulations in the field condition needs to be confirmed only after its toxicological behavior is studied. This information will help the regulating bodies to regulate its use in agriculture.

10.3.4 Synergistic/Antagonistic Effect of NPs on Herbicides

Some studies have evaluated the interaction effect of nanoparticles on herbicide, and they found both synergetic and antagonistic interaction. The silver nanoparticle (AgNPs) singularly, and in combination with Diclofop-methyl (DM) herbicide was evaluated. The results indicated that AgNPs alone has more impact on the plant growth, as compared to the mixture with herbicide. The antagonistic effect might be because the DM in solution affects the stability of AgNPs and reduced Ag+ release from AgNPs in the mixed solution (Li et al. 2018a). In another study, AgNPs have shown synergistic effect with imazethapyr (IM) (Wen et al. 2016). Combined exposure of AgNPs and herbicide in *Arabidopsis thaliana* had increased the silver concentration in roots. The exposure of AgNPs in plant has increased the accumulation of amino acids and resulting in more Ag+ formation from AgNPs (Wen et al. 2016).

10.4 Use of Nanoparticles for Removal of Herbicides from Soil and Water

Worldwide increasing trends of herbicide consumption and its contamination in soil and water are the major concerns for agricultural community (Hallberg 1986). The methods like photocatalysis and biological methods are being tested for efficient removal of these polluting herbicides from the water and soils. Popular solution to this problem can be the use of an efficient photocatalytic material for their degradation. Till date, several nanoparticles, such as TiO_2, Fe, ZnO, Si, or their composites, have been studied for degradation of organic compounds. Due to the eco friendliness, low cost, and novel properties, the nanocatalysts are gaining popularity. The NPs show properties like band gap in visible region, stability, and reusability. Some of the studies on nanoparticles in removing of herbicides have been discussed in detail below.

10.4.1 TiO_2 and Its Composites

The widely used catalyst TiO_2 is reported to be photochemically stable, non-toxic, and inexpensive. Therefore, the applicability of titania for remediation of pesticides from water was investigated (Daneshvar et al. 2006). In one study, the photocatalytic degradation of paraquat was achieved by TiO_2 nanoparticle that was synthesized by an acid-catalyzed sol–gel method (Marien et al. 2017). The results have shown that the catalytic performance of this composite was dependent on the morphology of particles. Also, it performed better in degradation of paraquat when compared to commercially available P25 nanoparticles. Similar results had been found in case of 2,4-D, when commercial TiO_2 is compared with hydrothermal TiO_2 (Sandeep et al. 2018). The biosynthesized TiO_2 NPs and hollow fibers, chemical synthesized TiO_2 nanotube arrays, and thin films had been used for paraquat degradation (Marien et al. 2016; Phuinthiang and Kajitvichyanukul 2018; Wongcharoen and Panomsuwan 2018; Zahedi et al. 2015), and results had confirmed that morphology of catalyst plays a key role in the photocatalytic activity.

Recently, many efforts are being made to convert the TiO_2 adsorption from UV to the visible light by doping with several transition metals, including platinum ions. The aim of these studies was focused on increasing catalyst degradation process efficiency under the solar spectrum. Efficient photodegradation of azimsulfuron in the presence of TiO_2 nanocrystalline films was achieved by using low-intensity black light tubes emitting in the near-UV. The degradation of the herbicide follows first-order kinetics according to the Langmuir–Hinshelwood model. The presence of platinum at neutral valence state and optimum concentration induced higher photodegradation rates, while silver-modified titania exhibited similar photocatalytic rates with those obtained with pure nanocrystalline TiO_2 films. Finally, the effect of initial pH value was also examined. Acidic or alkaline media were unfavorable for azimsulfuron photodegradation (Pelentridou et al. 2008). In another study with Sn-doped TiO_2 and commercially purchased TiO_2 P25, the photocatalytic degradation of a sulfonylurea herbicide-chlorsulfuron (ChS) was achieved. Comparison between these nanoparticles has indicated that presence of Sn^{4+} in the TiO_2 lattice has beneficial effect on the photocatalytic degradation of chlorsulfuron (Fresno et al. 2005).

The study was planned to check the feasibility of UV-assisted degradation of commonly used atrazine with TiO_2 nanoparticles doped with trivalent iron. Under the optimal condition, the maximum atrazine removal rate was achieved at pH = 11 in the presence of Fe^{3+}–TiO_2 catalyst (25 mg/L). The results obtained in this study suggested that this catalyst was an appropriate method to reduce atrazine in contaminated water resources up to 99% (Shamsedini et al. 2017). In previous study, sol–gel synthesis method was used to produce N,F-TiO_2 NPs, and this catalyst demonstrated three times more photoreactivity in atrazine degradation as compared to undoped TiO_2 (Samsudin et al. 2015). In another study, boron-doped TiO_2 was four times faster than those pure NPs for degradation of atrazine (Wang et al. 2016b). These doping has helped in effective interparticle electron transfer and resulted in more efficient catalyst.

In one study, the researchers have prepared platinum-modified TiO_2 samples and used them for photocatalytic degradation of 2,4-D and 2,4-DP herbicides (Abdennouri et al. 2015). The results of their study had proved the higher photocatalytic activity of Pt/TiO_2 as compared to bare TiO_2, and the photocatalytic activity increase was positively correlated to presence of the platinum in the catalyst mixture (Abdennouri et al. 2015). In another study, Pt was loaded in nanotube structured TiO_2 on Ti surface in ethylene glycol (Ti/TiO_2NTEG) was used for photo-electrocatalytic degradation of paraquat (Özcan et al. 2018), and the results indicated the better performance due to presence of Pt. Photocatalytic degradation of atrazine was evaluated by TiO_2 NPs that were superficially modified with Au, Ni, Cu NPs (Santacruz-Chávez et al. 2015). Out of these three catalysts, Au/TiO_2 has shown a better catalytic performance in similar reaction condition. It is also found that higher loading of metal ions on TiO_2 resulted in the lower photocatalytic activity, indicating that it needs to be standardized case by case (Yuliati et al. 2016). When Cu NPs incorporated TiO_2 nanotubes for degradation of Simazine—an herbicide used to kill control broad-leaved weeds and annual grasses, it was found that evenly distributed Cu (0.45%) on TiO_2 NTs was optimum to cause approximately 64% degradation in 4 h under UV light. Like other metals, the Cu acted as electron traps and prevented recombination of electron–hole pairs resulting in better photocatalytic activity (Meriam Suhaimy et al. 2016). One report has suggested that OH radical generated during the photocatalysis process by Bi-doped TiO_2 nanotubes anchored on graphene was mainly responsible for degradation of Dinoseb (Alam et al. 2017).

In another study, mesoporous Ga_2O_3–TiO_2 nanocomposites was synthesized with sol–gel method and used for degradation of imazapyr herbicide (Ismail et al. 2018). The experiments confirmed that the 98% of herbicide was degraded within 3 h when treated with 0.1% of catalyst. Another group of researchers used mesoporous In_2O_3–TiO_2 nanocomposites for photodegradation of same herbicide. They found 1.5% increase in photonic efficiency when nanocomposite was compared with TiO_2 (Kadi et al. 2018). Mesoporous titania/zirconia nanopowder was used for photocatalytic degradation of chloridazon (Mbiri et al. 2018). In another study, WO_3/TiO_2 and Fe_2O_3/TiO_2 were better catalysts for degradation of 2,4-D as compared with pure TiO_2 (Macías-Tamez et al. 2017). Mesoporous WO_3–TiO_2 nanocomposites with different WO_3 concentration (0–5 wt%) were used for 100% conversion of imazapyr (Ismail et al. 2016). These results also support earlier findings that addition of metal with TiO_2 shows stronger oxidative capability.

The carbon nanomaterials were also been used in synthesis of composite with TiO_2 for catalytic conversion of herbicides. In one study, the fullerene C60 with tetrahydrofuran and fullerenol nanoparticles was used to surface modification of

TiO_2, and the composite was used for mesotrione degradation under simulated sunlight. The TiO_2 with fullerenol nanoparticles showed the highest photo-activity, and addition of H_2O_2 and $KBrO_3$ as electron acceptors has resulted in better performance for mesotrione degradation (Djordjevic et al. 2018).

To overcome the problem associated with separation/recovery of TiO_2-based photocatalyst, many studies have reported the use of various support materials. The composite of Fe°/TiO_2 on activated charcoal (AC) was evaluated for photocatalytic degradation of 2,4-D. The results have shown that nanocomposite had possibility of recovery and reuse (Baloochi et al. 2018). With the aim to prepare the photocatalytic system with catalyst supported on some membrane, the researchers have used chitosan thin film for immobilization of TiO_2 (Le Cunff et al. 2015). The results of the study indicated that this composite has a potential and can be used in a variety of photoreactor designs. The resultant thin film was tested for photocatalytic treatment of terbuthylazine, and they found that this environmentally friendly material can be useful with negligible loss of TiO_2 activity during degradation reactions. Recently, a magnetic hexagonal mesoporous silica (magnetic HMS) was used to hold N-doped TiO_2, and this catalyst was used to remove three herbicides (trifluralin, 2,4-D, and glyphosate). The magnetic HMS and N-TiO_2 have shown a synergetic effect. Firstly, herbicide molecules were adsorbed on the surface of magnetic HMS and then the photodegradation by N-TiO_2 was achieved (Hosseini and Toosi 2018). Highly porous and permeable silicon carbide (SiC) foam was used with TiO_2 NPs for catalytic degradation of Paraquat (Marien et al. 2018). The SiC has properties like high chemical resistance and outstanding thermal stability. Its macro-porosity provided a huge surface for the immobilization of large amounts of TiO_2 photocatalyst. Natural zeolite–clinoptilolite was impregnated with TiO_2 NPs and used for the degradation of 2,4-D (Mehrabadi and Faghihian 2018). These results have provided possible materials for supported catalysis application.

In experimental condition, Bentazon herbicide has been successfully degraded by ZnO/TiO_2 nanocomposite under the UV light (Gholami et al. 2016). The results indicated that the neutral pH has shown better performance as acidic pH and alkaline pH have induced photocorrosion of ZnO. Removal efficiency of catalyst was more when O_2 was continuously purged along with addition of H_2O_2 into reaction mixture.

10.4.2 Fe and Its Composites

The laterite-based iron nanoparticles synthesized using eucalyptus leaf extracts were used as a catalyst for the degradation ametryn—a herbicide in aqueous medium (Sangami and Manu 2017). The results of study showed that optimum time required for degradation was 135 min with 2.83 mg/L dose if FeNPs and that proved the faster reaction kinetics in the presence of nanocatalysts. Similarly, teak plant extract was used to prepare FeNPs, which was used for oxidation of ametryn, dicamba, and 2,4-D mixture. The total conversion of herbicides was in 135 min when Fe NPs was added at the dose of 25.29 mg/L (Sangami and Manu 2018). In one study, it was postulated that sulfate radicals are the major agent of 2,4-D degradation during the hematite nanoparticle-activated peroxymonosulfate (Jaafarzadeh et al. 2017a).

The sulfentrazone is one of the preemergence and post-emergence weedicide for control of certain broadleaf weeds. In one study, the Fe/Ni nanoparticles were used for its dichlorination. Under the acidic pH (4.0), 1 gm/L of the nanoparticles achieved 100% degradation within 30 min. The conversion of sulfentrazone to lesser toxic substances was achieved by a direct reduction on the catalytic activity sites of nanomaterials and indirect reduction by atomic hydrogen (Nascimento et al. 2016). When Ni was used with core–shell Fe@Fe_2O_3 nanowires (CSFN) for degradation of atrazine, it increased the rate of conversion by six times (Shen et al. 2018). The finding has indicated that reduction of Ni produced active hydrogen (–H) that helped to break recalcitrant *s*-triazine ring, resulting in formation of formic acid and nitrite acid (Shen et al. 2018). Effectiveness of nanozerovalent iron (nano-ZVI) and palladium has been earlier assessed to dechlorinate herbicide atrazine from contaminated water and soil (Satapanajaru et al. 2008), and it was found that Pd has important role in catalytic process and enhanced destruction kinetic rates of atrazine. Composite comprising WO_3 with Fe-based MOF (MIL-53) has also exhibited outstanding photocatalytic efficiency for degradation of 2,4-D (Oladipo 2018). In recent study, α-Fe_2O_3 nanoparticles have been efficiently used for acetochlor degradation under the UV light (Fu et al. 2019).

Glyphosate is a popular choice of herbicide among the farmers due to its non-selective nature and has global presence. In recent study, reusable magnetic bismuth bromide oxide/ferrous oxide (BiOBr/Fe_3O_4) nanocomposites was used (Cao et al. 2019) for glyphosate degradation. It has reported that the degradation was almost double in case of composite when compared to pure BiOBr, and photo-generated holes (h+) were playing a major role in the photodegradation process. In one study, SBA-15 mesoporous silica-based material (Fe–NH_2–SBA-15) containing functionalized Fe NPs was used for removal of glyphosate from wastewaters (Rivoira et al. 2016).

The nano-ZVI when applied with biochar produced from maize was found that adsorption and degradation of 2,4-D were increased. In this study, 2,4-D was completed degraded after 40 h when Fe NPs and biochar were added at the rate of 0.33 and 0.17 g/L in soil medium. The biochar application avoided the aggregation and corrosion of Fe nanoparticles that resulted into better 2,4-D degradation (Ying et al. 2015). The nano-ZVI also found to be effective for degradation of metribuzin (a pre- and post-emergence herbicide) and alachor (K'Owino Isaac et al. 2018; Kabir et al. 2018). The poly(methacrylic-*co*-acrylonitrile) (p(MAc-*co*-AN)) microgels containing cobalt–iron (Co–Fe) bimetallic magnetic nanoparticles have been found to be very effective adsorbents for the removal of paraquat from liquid medium (Ajmal et al. 2015). Ordered mesoporous silicas-SBA-15 and KIT-6 were modified with iron by using the wet impregnation method. This nanostructured catalyst has been found effective degrade atrazine by heterogeneous photo-Fenton process (Benzaquén et al. 2018). Another nanocomposite containing nanoscale zero-valent iron (nZVI) on a clay mineral-attapulgite (ATP) was used to activate peroxymonosulfate (PMS) to generate reactive free radicals during the photocatalysis of for quinclorac (Ding et al. 2019).

In biodegradation, living microorganisms or their products are used to remove the pollutants. In case of herbicides also many potential microorganisms have been isolated for a cost-effective removal of contaminants. Some strains of *Bacillus* spp. can use atrazine as carbon and nitrogen source. Recently, two isolates of *Bacillus* spp. were immobilized on α-Fe_2O_3 magnetic NPs (Khatoon and Rai 2018). The results have shown that biodegradation efficiency was increased due to α-Fe_2O_3 magnetic NPs carrier. Due to immobilization, the physicochemical properties of biodegradation process can be extended, like pH (4.0–9.0), temperature (20–45 °C), initial concentration (50–300 mg L^{-1}), and agitation speed (50–300 rpm).

10.4.3 ZnO and Its Composites

Zinc oxide (ZnO) is also a widely used catalyst that shows efficient activity at low cost, so is widely used for pollutant degradation. In recent study, the two herbicide derivatives, metamitron and metribuzin, were exposed to photodegradation process assisted by Ag/ZnO composite (Xu et al. 2017). The Ag nanoparticle was present in every sheet of ZnO microflower, and the composite had shown the enhanced photocatalytic performance. This performance was accounted to the reduction of the recombination probability of electron–hole pairs due the presence of Ag that plays a critical role in photocatalysis. Similar results were obtained when Ag/ZnO powders had been used for degradation of diuron under solar light (Saidani et al. 2018). The results showed that addition of Ag helps to increase the rate of degradation by 14 times as compared to unmodified ZnO. When Ag and/or Au nanoparticles were added to Cu-doped ZnO, the photodegradation of diuron was significantly increased due to the synergistic effect by efficient electron transfer (Saidani et al. 2019). In one study, N-doped ZnO was used for degradation of 2,4-D and picloram under the on visible light. N-doping on ZnO shifted the photo-absorption wavelength range to longer wavelength, making it suitable for visible photocatalytic activity (Macías-Sánchez et al. 2015). Zinc oxide (ZnO) nanotube that was loaded with WO_3 nanoparticles was used for photodegradation of chlorinated phenoxyacetic acid. It has shown better efficiency as shown by other composites because of the improved separation of photo-generated charges (Li et al. 2018b). Biosynthesized ZnO was also tested for paraquat degradation (Munshi et al. 2018).

10.4.4 Other Nanoparticles/Composites

When researchers used combination of oxidants like peroxymonosulfate (PMS) and ozone, along with magnetic copper ferrite nanoparticles as a catalyst ($CuFe_2O_4$) for degradation of 2,4-D, it was found that 20.0 mg/L of 2,4-D could be completely degraded in 40 min. The reaction components were optimized in pH = 6.0, where the concentrations of PMS and ozone were 2.0 mM and 16.0 mg/L, respectively (Jaafarzadeh et al. 2017b). Zinc oxide nanoparticles alone were also used as catalyst for degradation of S-Metolachlor herbicide under the direct sun light (Rao et al. 2016).

A catalyst comprising of silver–tungsten oxide on porous siliceous SBA-15 (Ag-WO_3/SBA-15) support was used for degradation of atrazine in water samples. The photocatalytic degradation under visible light was significantly enhanced due to addition of Ag that resulted in reduction of electron–hole recombination (Gondal et al. 2016). WO_3 was coated on ZnO nanorods (NRs) and used for degradation of 2,4-D under natural sunlight. This catalyst has shown better performance as compared to pure ZnO NRs, and commercial WO_3, and might be due to the altered the optical properties (Lam et al. 2015). For 2,4-D, WO_3 nanorod doped with Pd was also effective photocatalyst, and activity was positively correlated with the quantity of doped Pd (Mkhalid 2016).

A catalyst comprising of Cu NPs on montmorillonite and quarts sand was also tested for atrazine degradation. The degradation of atrazine by montmorillonite and Cu NPs composite was found to be 1.7957 g mg^{-1} min^{-1}, while it was 0.8133 g mg^{-1} min^{-1} when Cu NPs was deposited on sand. The reaction rate was linked to redox-active species of Cu that are spread over the structure of composite (Kalidhasan et al. 2017). Cerium(IV) oxide (CeO_2) nanoparticles play a vital role in photocatalysis because the oxygen vacancies arise from multiple valency. In one study, the graphitic carbon nitride/CeO_2 (g-C_3N_4/CeO_2) composite was utilized for degradation of diuron, and the results indicated the good performance of the catalyst under the visible light. The better performance of this composite was due to the enhanced separation efficiency of photo-induced electron–hole pair by forming heterojunction between ceria and g-C_3N_4 (Kesarla et al. 2018). When two semiconductors—CeO_2 and Sb_2S_3—were used with chitosan/starch support for degradation of Paraquat under the UV light, it was found that hydroxide form present in the composite produced more –OH. Also the heterostructured NPs influenced the band gap of the product resulting in better performance (Hosseini et al. 2018).

Nanostructured bismuth oxide has shown a strong potential for photocatalytic degradation of pollutants in aqueous medium. When different sizes of Bi_2O_3 nanoparticles were used for atrazine degradation, the results suggested that particle size effect is very important factor that needs to be considered while developing a Bi_2O_3-based catalyst system (Sudrajat and Sujaridworakun 2017). A composite of manganese dioxide/graphite (MnO_2/C) was synthesized by high-energy electron beam irradiation. This synthesis method introduced large number of hydroxyl groups on MnO_2 nanosphere surface. These hydroxyl groups increased the adhesion of MnO_2 on graphite by hydrogen bond and were mainly responsible for the catalytic degradation of glyphosate through hydroxyl radicals (Wang et al. 2016a).

Recent years, graphene and graphene-based nanomaterials have gained immense interest as heterogeneous catalysts due to their properties like a larger surface area, high electrical conductivity, and excellent absorptivity. In one study, a composite consisting of $Ni_{0.8}Zn_{0.2}Fe_2O_4$ (NZF) nanoparticle and reduced graphene oxide (RGO) was used to degradation of trifluralin (Moitra et al. 2016).

Silica nanoparticles (SiNPs) are among the promising nanomaterials that have applications in the various fields like drug delivery, catalysis, immobilization, and sensing. They possess broad range of compatibility with the biosystems and can be easily synthesized. The application of silica nanoparticles for detection and degradation of herbicides is already highlighted in earlier reviews (Bapat et al. 2016; Nsibande and Forbes 2016). Palladium (Pd) nanoparticles when attached to carpet-like arrays of CNT that were anchored on porous carbon foams found effective in degradation of atrazine (Vijwani et al. 2018). The results indicated that this kind of hybrid structure can be used as potential platform for catalytic degradation. Also the green synthesized gold particles had also been used for highly efficient degradation of quinclorac (Shi et al. 2017).

10.5 Preparation of Nanomaterials Using Weeds

To generate develop any material to nanomaterials or create new materials, nanotechnology builds materials beginning with atoms that implemented through chemical, physical, and biological methods are used to produce nanoparticles which are reviewed earlier (Panigrahi et al. 2004). In recent past, the development of efficient green synthesis methods for nanoparticles has become a major focus of many studies. Many researchers have investigated the biological route to find an environment-friendly technique for producing well-characterized nanoparticles (Iravani 2011). The weeds which are available abundantly all over the word can be a very useful source of biotemplate for production of metal and other various nanoparticles. Some of the studies that have used weed for synthesis of nanoparticles are summarized in Table 10.1.

Many studied have used the extract of different tissues of weeds to synthesize particles like silver and gold (Table 10.1). In some studies, ZnO, iron, and palladium NPs had been synthesized. These biologically produced nanoparticles had shown potential application ranging from antimicrobial properties to catalyst for pollution degradation (Table 10.1). These studies provided a base for scaling up NPs synthesis by using freely available weed resources. This will open a possibility for its large-scale utilization for a rapid, non-polluting method of NPs synthesis.

Table 10.1 Green synthesis of different nanoparticles using weed extracts for various application

Nanoparticle	Weeds	Size	Application	References
Silver	Parthenium leaf extract	~50 nm	–	Parashar et al. (2009)
	Ipomoea aquatica, *Enhydra fluctuans* and *Ludwigia adscendens*	100–400 nm	–	Roy and Barik (2010)
	Desmodium triflorum	5–20 nm	Antimicrobial activity	Ahmad et al. (2011)
	Ipomoea carnea	–	Degradation of organic pollutants	Ganaie et al. (2014)
	Cannabis sativa (industrial hemp)	20–40 nm	Antimicrobial activity	Singh et al. (2018)
	Lepidium draba	20–80 nm	Antimicrobial activity	Benakashani et al. (2017)
	Mimosa pudica	10–60 nm	–	Ganaie et al. (2015)
	Lantana camara L.	~33.8 nm	Antibacterial activity	Manjamadha and Muthukumar (2016)
	Euphorbia hirta L.	40–50 nm	–	Elumalai et al. (2010)
	Solidago altissima	–	Plasmonic photocatalyst	Kumar et al. (2016)
	Chenopodium aristatum L.	3–36 nm	Catalytic/ Antibacterial activity	Yuan et al. (2017)
	Chenopodium murale	30–50 nm	Antioxidant and antibacterial activity	Abdel-Aziz et al. (2014)
	Chenopodium album	10–30 nm	–	Dwivedi and Gopal (2010)
	Malva parviflora	19–25 nm	–	Zayed et al. (2012)
	Prosopis juliflora	–	Antimicrobial activity	Raja et al. (2012)
	Lantana camara	–	Antimicrobial activity	Ajitha et al. (2015)
	Lantana camara	75.2 nm	Antioxidant activity	Kumar et al. (2015a)
	Trianthema decandra	36–94 nm	Antimicrobial activity	Geethalakshmi and Sarada (2012)
	Cynodon dactylon	8–10 nm	Antibacterial activity	Sahu et al. (2013)
	Lantana camara	~40 ± 2.8 nm	Antibacterial activity	Singh et al. (2015b)
	Calotropis procera	35 nm	–	Babu and Prabu (2011)
	Aerva lanata	~18.62 nm	Nanocatalysts	Joseph and Mathew (2015)
	Solanum nigrum	~28 nm	Antibacterial activity	Krithiga et al. (2015)

(continued)

Table 10.1 (continued)

Nanoparticle	Weeds	Size	Application	References
Gold	*Cannabis sativa*	12 and 18 nm	Antimicrobial activity	Singh et al. (2018)
	Tinospora cordifolia	16–75 nm	–	Abbasi et al. (2014)
	Mimosa pudica	–	Catalytic and antioxidant properties	Pirathiba et al. (2018)
	Pistia stratiotes L.	2–40 nm	–	Anuradha et al. (2015)
	Antigonon leptopus	–	Degradation of organic pollutants	Ganaie et al. (2016c)
	Chenopodium album	10–30 nm	–	Dwivedi and Gopal (2010)
	Prosopis juliflora	–	–	Raja et al. (2012)
	Trianthema decandra	33.7 nm and 99.3 nm	Antimicrobial activity	Geethalakshmi and Sarada (2012)
	Lantana camara	–	Dye Reduction	Phukan et al. (2018)
	Aerva lanata	~17.97 nm	Nanocatalysts	Joseph and Mathew (2015)
Silver-Gold	*Antigonon leptopus*	10–60 nm	–	Ganaie et al. (2016b)
Iron	*Eichhornia crassipes*, *Lantana camara* and *Mimosa pudica*	40–230 nm	Wastewater remediation	Prabhakar and Samadder (2017)
ZnO	*Parthenium hysterophorus* L.	Spherical and hexagonal particle, sizes 27 ± 5 nm and 84 ± 2 nm, respectively	Antifungal activity	Rajiv et al. (2013)
Palladium	*Antigonon leptopus*	5–70 nm	–	Ganaie et al. (2016a)

10.6 Conclusion

Nanotechnology is developing rapidly in recent years and producing new techniques, new structures, and new materials. This can act as the starting point for exploring nanotools in weed control. Many nanomaterials and nanostructures have biological properties against different types of weeds. In herbicide industry, many nanomaterials can be used in polymeric formulation. These nanoformulation materials' structure and property, and its stability are characterized to test the application with special properties. Designed nanoformulation using cheaper materials and that are more effective is required for reducing the product cost. The safety and environmental consideration for nanomaterials is another issue before its applications to overcome the traditional herbicides difficulties. Finally, we can conclude that nanotools are promising to change the field of weed control, ranging from the efficiency, good delivery systems and lower adverse effects on the environments. These technologies are in the early stage and can be used safely if many considerations taken into account.

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Chapter 11
Nanotools for Irrigation Water Remediation

Nidhi Chauhan, Utkarsh Jain and Shringika Soni

Abstract Water pollution and contamination removal have become a serious problem worldwide with a gradually increasing population. Conventionally, chemical precipitation, membrane filtration, flotation, ion exchange, adsorption, coagulation–flocculation and electrochemical methods are in use for drinking and wastewater purification. Nanotechnology has become an important tool in every aspect of water and environment remediation from the past few years. The unique structure and chemical property of nanocomposites help in water purification through pollutant adsorption, photoinhibition, nanocatalystic properties, transformation in less toxic materials and pathogen inactivation. Therefore, we have divided the chapter into three formats, in which first part will be discussing on Zn, Si, Cu, Ag, Ti, Fe, Pb, Zr and other metallic nanoparticles-based nanosorbent and nanocatalysts for toxic heavy metals and pathogen removal from water. We have also summarized several studies on biopolymer-based nanofiltration technique along with nanoscale zerovalent iron (ZVI) and zeolite conjugated nanomaterials for wastewater treatment. These nanomaterials not only proved their importance in water remediation, but also their unique characters in redox and self-stimulated reactions in contamination removal putting nanotechnology in top position. The second part of the chapter briefly explained nanotechnology-based commercialized techniques in water treatment and at last, future aspects in wastewater treatment scenario also perfunctory discussed.

Keywords Water pollution · Nanosorbent · Nanocatalysts · Nanofiltration

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11.1 Introduction

Water is one of the world's most abundant resources, but less than 1% of the global supply of water is available and safe for human consumption (Grey et al. 2013). According to the World Health Organization, over 760 million people were without adequate drinking water supply in 2011 (WHO 2013). Where it is available, the cost of potable water is rising due to increasing energy costs, growing populations and climatic or other environmental issues (Grey et al. 2013; Levin et al. 2002). The arid regions of North Africa and 70% population of European countries are confronted with extreme water shortage. Similarly, China is also facing this issue, since the main rivers for water supply are immensely polluted. Even with the advancement in water saving and purification, the USA is also showing the difficulty of exhausted water reservoirs as more water is extracted than refilled (Gehrke et al. 2015). In the Indian scenario, the Ministry of Urban Development (2013), Census 2011 and Central Pollution Control Board report expected that by around 2020, India will be a "water-stressed" country and by 2025 more than half of the world population will be facing water-based vulnerability. In addition, an increasing number of drinking water sources are showing evidence of contamination, especially by emerging pollutants like pharmaceuticals and personal care products (Houtman 2010; WHO 2012). Other contaminations include but not limited to heavy metal, toxic oil, pesticides, dyes, organic, inorganic compounds, endocrine disrupting compounds (EDCs) and plasticizers that may cause long-term effects.

From decades, we are using coagulation, flocculation, sedimentation, filtration and chlorine disinfection techniques to remove contamination, but these traditional wastewater treatment methods do not effectively remove emerging pollutants or are not capable of removing enough to meet increasingly stringent water quality standards (WHO 2012; Qu et al. 2012). Additionally, several technologies were developed over this time to meet complex end user goals which include aeration to control taste and odor, ion exchange and reverse osmosis for inorganic species removal and adsorption of organic species using activated carbon. In both developing and industrialized countries, a growing number of contaminants are entering the water bodies. The conventional decontamination processes like chlorination and ozonation consume a huge quantity of chemical agents and, furthermore, can produce toxic by-products. Contamination of surface waters also constitutes a risk to water supplies because pollutants may penetrate into aquifers, where they can be transported to drinking water sources. These challenges, among others, bring into focus the need for alternative water treatment and pollutant remediation methods to complement (Musico et al. 2014) or replace existing technologies.

With the growing demand for clean water sources, there is raising concern regarding the availability and strategies necessary for the contamination-free water. Therefore, nanoscale methodology for water treatment not only developed new techniques, they also improved conventional method like adsorption and membrane filtration at a new level. The focus of this chapter is to introduce nanotechnology-based techniques for water remediation which are required to understand and evaluate the severity of the current scenario. Besides the promising technological enhancements, the limitations of nanotechnology for water applications, such as laws and regulations as well as potential health risks, are reported. The commercially available water remediation techniques are also discussed in brief.

11.2 Nanotechnology in Water Remediation

Advances in nanoscale science and engineering are providing unprecedented opportunities to develop cost-effective and environmentally acceptable water purification processes. It is still in its infancy but holds promise in site remediating effectively and at very low cost. Metallic and carbonaceous nanoparticles, zeolites and dendrimers are the most commonly used nanomaterial in water purification processes that act via adsorption, redox reactions and catalysis and also act as a filtration membrane.

The small size pore, active redox reaction and lucrative property of nanocomposites are very helpful in removing contamination from water. Their catalytic activity for photochemical destruction of toxic contamination and ultrafiltration of organic and metallic compounds reported very helpful in groundwater and industrial sewage purification. We will be discussing the water purification mechanism-based ground and industrial wastewater treatment techniques.

11.2.1 Nanosorbent

The smaller size and large surface area enhance the adsorption and chemical properties of nanomaterials that play a key role in innate surface and external adsorption of metals or other contaminations in water (Gubin et al. 2005; Kalfa et al. 2009) (Table 11.1). It depends upon adsorption coefficient K_d and recitation partitioning of pollutants under equilibrium conditions (Hu et al. 2010; Mehrizad et al. 2011). The nanocomposites-based sorbent system needs to be environment-friendly, excellent adsorption capacity, reusable and must be separated easily (Sadegh et al. 2017), and magnetic nanocomposite conjugated nanosorbents demonstrated these qualities at a very higher extent.

Asgharinezhad and coworkers have used 4-(2-pyridylazo) resorcinol functionalized magnetic nanoparticles to adsorb 92 and 78 mg/g Cu(II) and Pb(II), respectively, with a limit of detection of 0.07 and 0.7 μg/L in a water sample (Asgharinezhad et al. 2014). Similarly, another magnetic nanocomposite, $Fe_3O_4@SiO_2@TiO_2$-based nanosorbent system was used in As(III) and As(V) adsorption within 4 h along with maximum adsorption capacity of 31.4 mg/g and 10.2 mg/g, respectively, at pH 9 (Feng et al. 2017a). Feng and his colleagues also developed ZrO_2-coated γ-Fe_2O_3-based nanosorbent system for affective removal of

Table 11.1 Nanocomposites-based sorbent system for wastewater remediation

S. no.	Nanosorbents	Contamination	References
1.	4-(2-pyridylazo) resorcinol functionalized magnetic NPs	Cu(II), Pb(II)	Asgharinezhad et al. (2014)
2.	Fe_3O_4@SiO_2@TiO_2	As(III), As(V)	Feng et al. (2017a)
3.	ZrO_2-coated γ-Fe_2O_3	As(III), As(V)	Feng et al. (2017b)
4.	ZnO@Ag_2O@Fe_3O_4	Cd(II)	Abdolmohammad-Zadeh et al. (2018)
5.	Fe_3O_4@SiO_2/SiCRG and Fe_3O_4@SiO_2/Si Starch	Paraquat	Fernandes et al. (2017)
6.	Melamine-based dendrimer amine (MDA) modified Fe_3O_4(MDA-Fe_3O_4)	Pb(II)	Sharahi and Shahbazi (2017)
7.	Quaternary amine-functionalized polymer, poly(glycidyl methacrylate) (PGMA)	Phenol and malathion	Younis et al. (2017)
8.	Nano-iron-oxide (Nano-Fe_3O_4) impregnated nano-sillicon oxide	Cu(II), Pd(II)	Mahmoud et al. (2013)
9.	Maghemite core and a silica porous layer-based magnetic permanently confined micelle arrays(Mag-PCMAs)	Acenaphthene, polycyclic aromatic hydrocarbon (PAH) and cadmium	Huang et al. (2016)
10.	Resin amberlite IR (AMIR) 120 H supported supermagnetic Fe_3O_4 nanoparticles	Cadmium	Goher et al. (2017)
11.	SDS conjugated amino-functionalized silica encapsulated magnetic iron-oxide micelle system	Organophosphates (OPs)	Hamedi et al. (2018)
12.	Isatin functionalized magnetic nanoporous SBA-15 nanosorbent	Cd(II), Ni(II), Pb(II) and Zn(II)	Dahaghin et al. (2018)
13.	γ-Al_2O_3-Silane-Cl nanosorbent	4-Nitroaniline (4NA) and 2-amino-3-nitropyridine (2A3NP)	Mahmoud et al. (2016)
14.	Zr-based amino-tagged metal organic framework (MOF), (UiO-66-NH_2)	2,4-DNP and 2,6-DNP (dinitrophenol)	Salimi et al. (2018)

As(III) and As(V) along with maximum adsorption capacity of 62.2 mg/g and 18.3 mg/g at pH 9 (Feng et al. 2017b). Abdolmohammad-Zadeh and colleagues demonstrated ZnO@Ag_2O@Fe_3O_4 nanocomposite-based nanosorbent system to extract Cd(II) from water samples with a detection limit of 0.03 ngm/L and sorption capacity of 48 mg/g (Abdolmohammad-Zadeh et al. 2018).

Polymer-based nanosorbents also exhibited biocompatibility and co-merge with samples without potential adverse effects of nanomaterials. The sorption capacity of polymer-based nanosorbents was reported to be enhanced after their conjugation with magnetic nanocomposites. In this direction, Fernandes et al. demonstrated $Fe_3O_4@SiO_2/Si$ coated natural polymers, κ-carrageenan (CRG) and starch-based nanosorbent system in paraquat removal from contaminated water with a comparatively higher adsorption capacity of $Fe_3O_4@SiO_2/SiCRG$ of 257 mg/g (Fernandes et al. 2017). Similarly, melamine-based dendrimer amine (MDA) modified Fe_3O_4(MDA-Fe_3O_4) nanosorbent system was also evaluated efficient Pb(II) removal from wastewater with a maximum adsorption capacity of 333.3 mg/g (Sharahi and Shahbazi 2017). In direction of not using magnetic nanoparticles, Younis et al. synthesized quaternary amine-functionalized polymer, poly(glycidyl methacrylate) (PGMA) for phenol and malathion pollutants adsorption from industrial and agricultural wastewater along with maximum adsorption capacity of 47.26 mg/g and 66.83 mg/g, respectively (Younis et al. 2017). They used green gamma radiation technology for nanosorbent development.

In continuation with magnetic nanosorbents, Mahmoud et al. used super magnetic nano-iron-oxide (Nano-Fe_3O_4) impregnated nano-silicon oxide nanosorbent system to Cu(II) and Pd(II) removal along with sorption capacity of 480 μmol/g of Cu(II) (Mahmoud et al. 2013). In another study, maghemite core and a silica porous layer-based magnetic permanently confined micelle arrays (Mag-PCMAs) were developed for acenaphthene, polycyclic aromatic hydrocarbon (PAH) and cadmium adsorption along with adsorption capacity up to 1060 mg/kg and 2250 mg/kg, respectively, at pH 6–9 (Huang et al. 2016). They also studied kinetics for calculating adsorption rate and isotherm studies for hydrophobic interaction between nanosorbent and contaminations. Similarly, resin amberlite IR (AMIR) 120 H supported super magnetic Fe_3O_4 nanoparticles-based nanosorbent system exhibited effective Cd removal from industrial wastewater along with maximum adsorption capacity of 307.04 mg/g at pH 7 (Goher et al. 2017). In another study, sodium lauryl sulfate (SDS) conjugated amino-functionalized silica encapsulated magnetic iron-oxide micelle system was used in effective removal as well as recovery of organophosphates from water and fruit juice samples (Hamedi et al. 2018). Dahaghin et al. also reported isatin functionalized magnetic nanoporous SBA-15 nanosorbent system to extract Cd(II), Ni(II), Pb(II) and Zn(II) with limits of detection of 0.10 ng/mL, 0.25 ng/mL, 0.4 ng/mL and 0.2 ng/mL and the maximum sorption capacity of 140, 122, 110 and 115 mg/g, respectively (Dahaghin et al. 2018). This nanosorbent system was proved very efficient in a trace amount of Cd(II), Ni(II), Pb(II) and Zn(II) removal in water and agricultural field.

Some researchers have developed γ-Al_2O_3-silane-Cl nanosorbent system for effective removal of 4-nitroaniline (4NA) and 2-amino-3-nitropyridine (2A3NP) for tap water, sea water and wastewater along with maximum adsorption capacity of 96.85–99.06 mg/g (Mahmoud et al. 2016). In another study, Zr-based amino-tagged metal organic framework (MOF), (UiO-66-NH_2), nanosorbent was developed to extract 2,4-DNP and 2,6-DNP (dinitrophenol) in environmental water samples (Salimi et al. 2018).

11.2.2 Nanocatalysts

Other than size and shape, nanomaterials have a unique place in water purification due to its optical/electronic and catalytic properties via redox mechanism. The photocatalytic, electrocatalytic and fenton-based catalytic properties of nanomaterials opened a new door in effective water purification methods (Table 11.2). Till now ZnO and TiO_2 are the most common and widely applicable nanomaterial due to its high reactivity under UV and high chemical stability; but due to its high energy gap further modifications were performed for proper water pollutants degradation (Akhavan 2009; Lin et al. 2014). Several researchers reported photocatalytic property of TiO_2 and its conjugates in degradation of methylene blue, rhodamine B, methyl orange and other pharmaceutically active compounds like propranolol, diclofenac and carbamazepine in wastewater (Chen et al. 2015; Lin et al. 2015; Guan et al. 2016; He et al. 2016a, b). The metallic doping or modifications of these photocatalysts were also reported in wastewater purification in recent years. In this direction, Sathishkumar and colleagues, 2011 reported degradation of textile wastewater dye under the photocatalytic treatment of CuO and ZnO nanocomposites (Sathishkumar et al. 2011). Similarly, organic homopolymer polyaniline (PANI) modified ZnO nanocomposite was observed to degrade methylene blue and malachite green dyes in photocatalytic treatment of organic pollutants in wastewater (Eskizeybek et al. 2012). Ranjith et al. have also developed 1-D multifunctional ZnO nanorods on 2-D reduced graphene oxide (rGO) sheets nanocomposite for wastewater treatment. This nanocomposite degraded methylene blue (MB), methyl orange (MO) and rhodamine B (RhB) under visible light irradiation and adsorbs Cu^{2+} and Co^{2+} ions from water sample (Ranjith et al. 2017). In another similar study, Mohamed and his team have developed polypyrrole fabricated Zn–Fe nanoparticles-based photocatalytic water degradation (Mohamed et al. 2018). They introduced interfacial polymerized polypyrrole on the surface of Zn–Fe layer double hydroxide (PPy NF@Zn Fe LDH) and studied the adsorption and photocatalytic property of the composites to excise the safranin dye from water.

Due to the importance of magnetic nanoparticles in catalytic activity, they were widely in use to separate pollutants from water from several decades. The nanoferrites, maghemite nanoparticles (Fe_2O_3) and maghemite/silica nanocomposite (Fe_2O_3/SiO_2) were reported to act as nanocatalysts with their unique properties of stability toward uncontrolled oxidation of pollutant and organic intermediate products in water remediation (Shahwan et al. 2011; Ferroudj et al. 2013). In the direction of oil spill remediation and organic adulterant removal, several researches have been focused on the use of nanocomposites. The non-reducing cyclic oligosaccharides-coated superparamagnetic iron-oxide nanoparticles (SPION) core–shell nanocomposite was reported in oil spill remediation and bisphenol A (BPA) removal from wastewater (Kumar et al. 2015a). This nanocomposite demonstrated 7.2 g/g retention capacity and 82.5% photodegradation of the organic BPA under solar light illumination. In another study, Ti and Fe mixed clay

Table 11.2 Photocatalytic activity of nanocomposites in wastewater remediation

S. no.	Photocatalytic nanocomposites	Contamination	References
1.	CuO and ZnO	Textile wastewater dye	Sathishkumar et al. (2011)
2.	Organic homopolymer polyaniline (PANI) modified ZnO nanocomposite	Methylene blue and malachite green dyes	Eskizeybek et al. (2012)
3.	1-D multifunctional ZnO nanorods on 2-D reduced graphene oxide (rGO) sheets nanocomposite	Methylene blue (MB), methyl orange (MO), rhodamine B (RhB), Cu^{2+} and Co^{2+} ions	Ranjith et al. (2017)
4.	Interfacial polymerized polypyrrole on the surface of Zn–Fe layer double hydroxide (PPy NF@Zn Fe LDH)	Safranin dye	Mohamed et al. (2018)
5.	Non-reducing cyclic oligosaccharides-coated superparamagnetic iron-oxide nanoparticles (SPION) core–shell nanocomposite	Bisphenol A (BPA)	Kumar et al. (2015a)
6.	TiO_2- and Fe_2O_3-halloysite nanocomposites	Aniline and its chloro derivatives	Szczepanik et al. (2017)
7.	Fe_2O_3–Mn_2O_{33} nanocomposite	As(III)	Eslami et al. (2018)
8.	Metallic $CuCr_2O_4$ decorated g-C_3N_4 nanosheets (g-C_3N_4-NS/$CuCr_2O_4$)	RhB, MB and phenol degradation	Akhundi and Habibi-Yangjeh (2017)
9.	3-D crystalline g-C_3N_4 and graphene nanosheets	MB, MO and bromate	Tang et al. (2017)
10.	Ag coated g-C_3N_4 nanocomposite	Sulfamethoxazole (SMX)	Song et al. (2018)
11.	Molybdenum disulfide (MoS_2) conjugated 2-D g-C_3N_4 and graphene nanoparticles	Methylene blue (MB), rhodamine B (RhB), crystal violet (CV) and heavy toxic Cr (IV)	Wu et al. (2018)
12.	Graphitic-C_3N_4@nickel–Aluminum-layered double hydroxide (g-C_3N_4@NiAl-LDH NCPs)	RhB and MO dyes	Salehi et al. (2018)
13.	Au coated aurivillius oxide (Bi_2WO_6)	Cr(VI)	Yang et al. (2015)
14.	BiOI-BiOCl/g-C_3N_4 nanocomposite	Acid orange 7 (AO 7)	Aghdam et al. (2017)
15.	BiOI/NiO-based nanocomposite (p-BiOI and p-NiO)	Acid orange 7 (AO 7)	Yosefi and Haghighi (2018)
16.	Bismuth ferrite (BFO) nanoparticles, $BiFeO_3$/$Bi_{25}FeO_{40}$	Acid Yellow (AY-17) and Reactive Blue (RB-19) dyes	Kalikeri and Shetty (2018)

(continued)

Table 11.2 (continued)

S. no.	Photocatalytic nanocomposites	Contamination	References
17.	Ag coated bismuth vanadate ($BiVO_4$) nanocomposite	*E. coli*, *E. faecalis* and *F. solani spores*	Booshehri et al. (2017)
18.	TiO_2–Fe_2O_3 nanocomposites	*E. Coli*	Sharma et al. (2018)

nanocomposites exhibited excellent adsorptive property for inorganic ions. The TiO_2- and Fe_2O_3-halloysite nanocomposites showed a significant difference in photodegradation of aniline and its chloro derivatives from wastewater comparative to commercially available photocatalytic TiO_2 or halloysite containing TiO_2 (Szczepanik et al. 2017). The Fe_2O_3–Mn_2O_3 nanocomposite was also investigated for their photocatalytic oxidation and adsorption property for As(III) removal under UV light illumination (Eslami et al. 2018).

Not restricted to this, several researchers developed nanocomposites conjugated metallic nanoparticles for water remediation. Akhundi and Habibi-Yangjeh designed metallic $CuCr_2O_4$ decorated g-C_3N_4 nanosheets, g-C_3N_4-NS/$CuCr_2O_4$ (10%), in RhB, MB and phenol degradation under visible light (Akhundi and Habibi-Yangjeh 2017). This study also exhibited the strong photocatalytic activity of $CuCr_2O_4$ due to its low band gap and co-catalyst property of g-C_3N_4 nanosheets in water pollutant removal. In another study, 3-D crystalline g-$C_3N_4$and graphene nanosheets composite demonstrated extraordinarily photocatalytic activity for MB, MO and bromated in water treatment under visible light illumination (Tang et al. 2017). Similarly, Ag coated g-C_3N_4 nanocomposite was used for photocatalytical removal of sulfamethoxazole (SMX), with a removal efficiency of 32.1%, under visible light irradiation for surface water (Song et al. 2018). Wu et al. also used light absorbing property of the layered structure of molybdenum disulfide (MoS_2) and catalytic property of 2-Dg-C_3N_4 and graphene nanoparticles in water purification (Wu et al. 2018). These nanocomposites exhibited photocatalytic elimination of organic dyes, methylene blue (MB), rhodamine B (RhB), crystal violet (CV) and heavy toxic Cr(IV) from contaminated water. In direction of polymer-based water remediation techniques, Salehi et al. have also used graphitic-C_3N_4@nickel–aluminum-layered double hydroxide (g-C_3N_4@NiAl-LDH NCPs) nanocomposites for photocatalytic degradation of RhB and MO dyes in contaminated water samples (Salehi et al. 2018).

Instead of these advancements, researchers demonstrated catalytic property and low toxicity of bismuth salts in wastewater treatment. Yang and team have reported gold coated simplest aurivillius oxide (Bi_2WO_6) in alcohol oxidation and Cr(VI) reduction in wastewater remediation under visible light (Yang et al. 2015). They also supported reducing property of gold ion via exhibiting the photocatalysis of the water pollutant at 2 wt% and 1 wt% of Au/Bi_2WO_6. The BiOI-BiOCl/g-C_3N_4 composite was also reported for photocatalytic degradation of acid orange 7 with 97.4% degradation efficiency in the presence of visible light (Aghdam et al. 2017).

Similarly, BiOI/NiO-based nanocomposite was successfully fabricated for photocatalytic degradation of acid orange 7 (AO7), and the mechanism of water remediation was studied via staggered band gap alignment between p-BiOI and p-NiO for coherent control of the recombination of photogenerated charge carriers (Yosefi and Haghighi 2018). In continuation, mixed-phase bismuth ferrite (BFO) nanoparticles, $BiFeO_3/Bi_{25}FeO_{40}$, demonstrated UV and visible light-mediated photocatalytic atrophy of Acid Yellow (AY-17) and Reactive Blue (RB-19) dyes in water samples under acidic condition (Kalikeri and Shetty 2018).

Other than dyes and metallic pollutants, several studies have focused on microorganisms' decay from wastewater. Booshehri and team have evaluated the photocatalytic property of bismuth vanadate ($BiVO_4$) for water disinfection (Booshehri et al. 2017). They used Ag coated $BiVO_4$ nanocomposite under visible solar light for inactivation of *E. coli, E. faecalis and F. solani spores*. In a similar study, Sharma et al. have used different ratios of TiO_2–Fe_2O_3 nanocomposites in photocatalytic inactivation of *E. Coli* in water sample under natural solar light irradiation (Sharma et al. 2018).

11.2.3 Nanofiltration

Among the several advanced water treatment techniques, nanotechnology-based membrane filtration technology is considered as the most effective and sensitive approach. This technique is very economical, simple in design, very efficient and did not compromise with water quality (Zhang et al. 2015; Guo et al. 2016) (Table 11.3). Among the electrodialytic membrane, polymer membrane, ultrafiltration membrane, liquid membrane and nanofiber membrane, the most common nanofiltration is extensively applied in wastewater treatment due to its small pore size and user-friendliness (Ouyang et al. 2013; Rashidi et al. 2015). The superior mechanical and chemical properties of thin film nanocomposite membrane also opened new dimensions in nanofiltration and reverse osmosis membrane to separate contaminations from water (Lind et al. 2010).

On other hand, silver, titanium and its oxide's nanoparticles-based thin film filtration membranes were proved to have antimicrobial, UV active and low fouling property during industrial water treatment (Lee et al. 2008; Goyal et al. 2011). The aquaporin protein-based membrane filtration proved itself very promising in wastewater treatment. The high permeability and high specificity of aquaporin-based symmetric poly-(2-methyloxazoline)-poly-(dimethylsiloxane)-poly-(2-methyloxazoline) (PMOXA 15–PDMS110–PMOXA 15) triblock copolymer vesicles showed 100 times higher permeability coefficients compared to commercially available RO membrane (Kumar et al. 2007).

Nanocomposites-based filtration method is the latest method in which nanofillers are embedded in polymeric or inorganic oxide matrix base for water treatment. Several nanocomposites of metallic nanoparticles (TiO_2, Al_2O_3), antimicrobial

Table 11.3 Nanofiltration membrane in water remediation

S. no.	Nanofilteration membrane	Contamination	References
1.	Aquaporin-based symmetric poly-(2- methyloxazoline)-poly-(dimethylsiloxane)-poly-(2-methyloxazoline) (PMOXA 15–PDMS110–PMOXA 15) triblock copolymer	Wastewater	Kumar et al. (2007)
2.	GO surface-deposited poly (amideimide)-polyethyleneimine(PAI-PEI) hollow fiber membrane nanofilter	Wastewater	Goh et al. (2015)
3.	Block copolymers (BCPs) dispersed CNT intercalated rGO modified nanofiltration	Nanoparticles, dyes, peptides, OPs, sugars and humic acid	Chen et al. (2016a)
4.	Carbon matrix imbedded polyethersulfone (PES) polymer-based nanofiltration	Copper and sulfate	Hosseini et al. (2018)
5.	CO_2 responsive positively charged poly (N,N-diethylaminoethyl methacrylate) (PDEAEMA) polymer conjugated GO nanofiltration membrane	$MgCl_2$	Dong et al. (2018a)
6.	Aluminum sulfate modified hollow fiber nanofilters	Activated carbon and humid substance	Kohler et al. (2016)
7.	Chitosan associated nanofiltration membrane	Alkalinity and calcium ions	Ang et al. (2016a)
8.	Coagulant pretreated NF 270 nanofiltration membrane	Brackish water in calcium salt and foulants precipitation	Ang et al. (2016b)
9.	MWCNT/Fe_2O_3 conjugated ultrafiltration	Bisphenol A (BPA) and norfloxacin (NOR)	Wu et al. (2016)
10.	Magnetic ion exchange resin (MIEX)-based nanofiltration system	–	Imbrogno et al. (2018)
11.	Multistage nanofiltration (NF)–forward osmosis (FO)–reverse osmosis (RO) system	Brackish water	Altaee and Hilal (2015)
12.	Serinol (2-amino-1,3-propanediol) modified thin film composite NF	Ca^{2+}, Mg^{2+} and SO_4^{2-} in polymer flooding produced water (PFPW)	Zhang et al. (2017a)

nanoparticles (nanosilver and CNTs), bimetallic nanoparticles as photocatalytic nanomaterials, in combination with zeolites were also reported to improve the water permeable flux and resistance to fouling in groundwater (Gehrke et al. 2015). In this direction, Goh et al. developed GO surface-deposited poly(amideimide)-polyethyleneimine (PAI-PEI) hollow fiber membrane nanofilter from which 86% pure water was obtained (Goh et al. 2015). The use of excellent water permeability, anti-fouling and anti-bacterial properties of GO along with PAI derived polyimide functional groups in-between the filtration membrane was proposed for large-scale water softening applications. In continuation of using polymer-based nanofiltration, block copolymers (BCPs) dispersed CNT intercalated rGO modified nanofiltration membrane was used in the removal of nanoparticles, dyes, peptides, OPs, sugars and humic acid along with high retention efficiency, excellent anti-fouling and permeability capacities (Chen et al. 2016a, b).

Several other studies have been also carried out in direction of polymer-based nanofiltration membrane development in water remediation. Hosseini et al. have designed mixed carbon matrix imbedded polyethersulfone (PES) polymer-based NF in copper and sulfate removal from wastewater (Hosseini et al. 2018). This filtration system showed 95% sulfate and 97% copper removal within the use of 0.5 wt% nanoparticles onto NF although only 0.1 wt% amount of nanoparticles caused increased water content in the membrane and the porosity. In another study, CO_2 responsive positively charged poly(N,N-diethylaminoethyl methacrylate) (PDEAEMA) polymer conjugated GO nanofilteration membrane was used in $MgCl_2$ removal along with excellent gas-tunable water permeability (Dong et al. 2018a).

Kohler and team have also developed aluminum sulfate modified hollow fiber nanofilters in large drinking water treatment plant in Sweden. Their coagulant associated nanofiltration system was reported to reduce 8.7 mg C/L activated carbon to 0.5 mg C/L, 6510 μg C/L humid substance to 140 μg C/land 260 μg C/lto 10 μg C/L polymers in surface water (Kohler et al. 2016). Similarly, chitosan (natural coagulant) associated nanofiltration membrane was also demonstrated a reduction in alkalinity and calcium ions in saline water samples, but the charge neutralization property of chitosan on nanofiltration enhanced fouling propensity of the membrane (Ang et al. 2016a). In another study, Ang et al. used coagulant pretreated NF 270 nanofiltration membrane in brackish water in calcium salt and foulants precipitation for water remediation (Ang et al. 2016b).

Other than these studies, magnetic MWCNT/Fe_2O_3 conjugated ultrafiltration membrane was also studied in bisphenol A (BPA) and norfloxacin (NOR) removal from drinking water along with the effect of pH, ionic strength, initial concentration and transmembrane pressure (TMP) on water remediation process (Wu et al. 2016). Imbrogno end colleagues reported magnetic ion exchange resin (MIEX)-based nanofiltration system to enhance the water purity due to higher kinetics of organic matters and more active exchange sites of MIEX and small size and larger surface area of MIEX-NF drinking water remediation system (Imbrogno et al. 2018).

A multistage nanofiltration (NF)–forward osmosis (FO)–reverse osmosis (RO) system also demonstrated > 90% recovery in brackish water treatment (Altaee and Hilal 2015). Zhang et al. also designed serinol (2-amino-1,3-propanediol) modified thin film composite NF Ca^{2+}, Mg^{2+} and SO_4^{2-} in polymer flooding produced water (PFPW) (Zhang et al. 2017a, b).

11.2.4 Zeolites

Zeolites are naturally occurring alumino silicate group with high adsorption, cations exchange capacity and hydration–dehydration properties. Their high surface area and high chemical and mechanical resistance make them extremely effective ion exchangers in water purification (Damjanović et al. 2010; Goyal et al. 2011). The large number of accessible active sites on zeolites results more hydrophobic characteristic and water capacity of molecular sieves that helps in water remediation (Table 11.4).

Naturally occurring zeolite like clinoptilolite and chabazite were reported to remove radioactive ^{90}Sr and ^{137}Cs from liquid nuclear waste and toxic metals from groundwater (Rhodes 2010). The acid-modified clinoptilolite zeolite was also

Table 11.4 Nanocomposites conjugated zeolites for wastewater treatment

S. no.	Nanocomposite decorated zeolite	Contamination	References
1.	TiO_2 loaded haydite, silica-gel-based zeolite and clinoptilolite	Ammonia	Wang et al. (2007), Damjanović et al. (2010)
2.	Zeolite A (LTA) and NaP1 zeolites, (Na_6Al_6 $Si_{10}O_{32}$, $12H_2O$)	Pb^{2+} and Cr^{3+} ions	Muhammad and Munawar (2007)
3.	Clinoptilolite and chabazite	^{90}Sr and ^{137}Cs	Rhodes (2010)
4.	MgFe decorated natural zeolite in shell–core system, covered with layered double hydroxides (LDH)	NH^{4+}–N and 83.29% total phosphorus (TP)	Guo et al. (2015a)
5.	Fe(II)-modified zeolites (ATZ, ZS-500RW and ZEOSAND)	Hexavalent Cr(VI)	Lofu et al. (2016)
6.	NaP1 zeolite	Cr^{3+}, Ni^{2+}, Zn^{2+}, Cu^{2+} and Cd^{2+} from acid mine and electroplating wastewater	Alvarez-Ayuso et al. (2003)
7.	ZSM-5(MFI) ($Na_nAl_nSi_{96-n}O_{192} \approx 16H_2O$)	–	Pendergast and Hoek (2011)
8.	Al-modified clinoptilolite	Ammonium	Vocciante et al. (2018)
9.	Zeolite incinerator ash (ZIA)	anthracene, phenanthrene, pyrene and dyes	Mateen et al. (2015)
10.	Cationic cetyltrimethylammonium bromide (CTMAB) and cetylpyridinium bromide (CPB) modified zeolite	Pb(II) and Cr(II)	Ren et al. (2016)
11.	MWW zeolites, MCM-22, MCM49, MCM-56 and Ce/MCM-22	Alcohols	Gil et al. (2018)
12.	3-D Yemeni zeolites	Ammonium	Jmayai et al. (2018)

reported for the build-in-dual capacity of desalination of Na^+ removal (40–85% from saline water and 73–87% groundwater) and pH neutralization in saline and groundwater (Paul et al. 2017). TiO_2 loaded haydite, silica-gel-based zeolite and clinoptilolite alone were also developed for ammonia removal from water (Wang et al. 2007; Damjanović et al. 2010). Some artificial zeolites, like zeolite A (LTA) and NaP1 zeolites ($Na_6Al_6\ Si_{10}O_{32}$, $12H_2O$), were observed to remove toxic material Pb^{2+} and Cr^{3+} ions from water (Muhammad and Munawar 2007).

In another studies, magnetic nanoparticle-based zeolites demonstrated the removal of heavy metal like Pb^{2+}, As^{3+} and vanadium (V) from wastewater with removal efficiency more than 70% (Attia et al. 2014; Mthombeni et al. 2015; Visa 2016). These natural and artificial zeolites were combined with membrane filtration method to enhance the water treatment techniques. Guo and team developed a core–shell zeolite system for water remediation. They designed MgFe decorated natural zeolite in the shell–core system and covered with layered double hydroxides (LDH) in municipal wastewater treatment with a maximum adsorption capacity of 79.3651 mg/kg for 81.50% NH^{4+}–N and 83.29% total phosphorus (TP) removal (Guo et al. 2015a, b). In continuation of this, Lofu et al. have also used Fe(II)-modified zeolites (ATZ, ZS-500RW and ZEOSAND) for removal of toxic hexavalent Cr(VI) in contaminated water in which all zeolites proved their efficiency for the Cr(VI) capturing and ZEOSAND reported to be more stable in higher pH conditions (Lofu et al. 2016).

A number of researchers have developed metal conjugated ZVI for industrial and drinking water treatment. The NaP1 zeolite evaluated to remove Cr^{3+}, Ni^{2+}, Zn^{2+}, Cu^{2+} and Cd^{2+} from acid mine and electroplating wastewater (Alvarez-Ayuso et al. 2003). Similarly, Pendergast and colleagues reported metallic conjugated zeolite ZSM-5 (MFI) ($Na_nAl_nSi_{96\text{-}n}\text{-}O_{192} \approx 16H_2O$ ($n \approx 3$))-based nanomembrane of aqueous osmotic separation of water (Pendergast and Hoek 2011). In another study, Al-modified clinoptilolite was taken under consideration for ammonium adsorption in groundwater remediation (Vocciante et al. 2018).

In the direction of heavy metallic and toxic hydrocarbons removal, Mateen et al. have used zeolite incinerator ash (ZIA) industrial wastewater treatment (Mateen et al. 2015). The 1 mg/kg amount of ZIA exhibited 98, 97 and 96% removal efficiency of anthracene, phenanthrene and pyrene as well as 90% removal of dyes via adsorption in industrial water. In another study, Ren et al. have used cationic cetyl trimethyl ammonium bromide (CTMAB) and cetyl pyridinium bromide (CPB) modified zeolite for Pb(II) and Cr(II) removal via adsorption (Ren et al. 2016). Chen and colleagues also designed Ce, Fe or Mn oxides loaded ZSM5 zeolite for treating refractory wastewater. They used metallic oxide loaded NaZSM5-38, HZSM5-38 and NaZSM5-100 zeolites for nitrobenzene removal from the water via catalytic ozonation processes (COP) (Chen et al. 2018). Similarly, Gil et al. have used catalytic properties of MWW zeolites, MCM-22, MCM49, MCM-56 and Ce/MCM-22, in tetrahydropyranylation of alcohols for water remediation (Gil et al. 2018). Researchers also studied regional-specific 3-D Yemeni zeolites for industry and urban wastewater treatment via evaluating the kinetics of zeolite and ammonium adsorption (Jmayai et al. 2018).

11.2.5 Nanoscale Zerovalent Iron (ZVI)

This iron nanoparticle-based technique has its core made up of zerovalent or metallic iron, and the shell is composed of mixed valent [Fe(II) and Fe (III)] oxides at 10–100 nm in size. The large surface area, more reactive sites along with dual properties of adsorption and reduction make the ZVI very valuable in water remediation (Bhattacharya et al. 2013) (Table 11.5). Several researchers have been reported usability of ZVI in removing heavy metal, organic and inorganic pollutants from groundwater. Nanoscale ZVI is not only effective to remove colored humic acid, toxic chlorinated organic compounds, pesticides, organic dyes, etc. (Amin et al. 2014; Adeleye et al. 2016), but they also played an important role in oxidize pharmaceutical products like amoxicillin, ampicillin, ibuprofen and metronidazole from wastewater (Ghauch et al. 2009; Machado et al. 2013; Fang et al. 2010). Recent studies of nZVI mainly focused in the dechlorination of contamination of wastewater. Wu and his team designed ZVI supported cellulose acetate membrane to dechlorinate the chlorinated olefins and paraffins from polluted water. On the other hand, nanomaterials conjugated ZVI composites also demonstrated contamination removal form wastewater. Arsenic [As(0), As(II) and As(V)] (Mauricio 2010), Mn-doped Al-based bi-metal oxides (Wu et al. 2014), Zr-modified MgFe-layered double hydroxide carbonates (Chitrakar et al. 2010) and ZrO_2-coated graphite oxide (Zong et al. 2013) conjugated nZVI were reported its significance in arsenic and phosphate removal from seawater and in situ condition.

In this direction, Pd/Fe nanoparticles incubated nZVI was reported to degrade 80–90% pentachlorophenol (PCP), polychlorinated aromatic compound via adsorption process (Tso and Shih 2015). The heterogeneous Fenton/Fenton-like catalyst activity of ZVI was reported to degrade toxic pollutant in wastewater. Further, the sulfide-modified nZVI (S-nZVI) was also reported for optimal 95% Cd removal capacity at pH 5 of different contaminated water matrices (Su et al. 2015). Lin et al. have also used acid-washed zero valent aluminum (ZVAI) in the successful removal of bromide at 60 °C at pH 3 via adsorption process, while it was completely ineffective in alkaline solution (Lin and Lin 2016). This nanocomposite specifically selects bromide-based pollutant over nitrate in wastewater and reusability of the ZVAI exhibited their importance in water remediation technology. Arvaniti et al. have designed Mg-aminoclay (MgAC)-coated nZVI for effective removal of perfluorinated compounds (PFCs) micropollutants in wastewater (Arvaniti et al. 2015). They evaluated removal efficiency of MgAC-nZVI for four PFCs (PFOA, PFOS, perfluorononanoic acid; PFNA and perfluorodecanoic acid; PFDA) via surface adsorption and reduction via dehydrohalogenation at pH 3 and low reaction temperature. Adio et al. have used biosynthesized nanoscale ZVI (100 mg) for effective 95% and 90% removal of arsenic (As) and selenium (Se) from wastewater at pH 3 (Adio et al. 2017). In another study, bimetallic nano-Fe/Cu particles and nZVI conjugated system were used in efficiently to adsorb cesium from contaminated water (Shubair et al. 2018).

Table 11.5 Nanoscale zerovalent iron-based nanosystems for water purification

S. no	Nanocomposite decorated zeolite	Contamination	References
1.	Mg-aminoclay (MgAC)-coated nZVI (MgAC-nZVI)	Perfluorinated compounds (PFCs: (PFOA, PFOS, perfluorononanoic acid; PFNA and perfluorodecanoic acid; PFDA))	Arvaniti et al. (2015)
2.	Pd/Fe nanoparticles incubated nZVI	Pentachlorophenol (PCP), polychlorinated aromatic compound	Tso and Shih (2015)
3.	Sulfide-modified nZVI (S-nZVI)	Cadmium	Su et al. (2015)
4.	Zero valent aluminum (ZVAI)	Bromide- and nitrate-based water pollutants	Lin and Lin. (2016)
5.	Mg-amino clay (MgAC)-coated nZVI	PFCs (PFOA, PFOS, perfluorononanoic acid; PFNA and perfluorodecanoic acid; PFDA)	Arvaniti et al. (2015)
6.	Biosynthesized nanoscale ZVI	Arsenic (As) and selenium (Se)	Adio et al. (2017)
7.	Bimetallic nano-Fe/Cu particles and nZVI	Cesium	Shubair et al. (2018)
8.	Iron supported nZVI on activated carbon (nZVI/AC)	Nitrate and phosphate	Khalil et al. (2017)
9.	ZVI/Cu bimetallic catalyst	Azo-dye orange II	Yamaguchi et al. (2018)
10.	Pederr sulfate modified ZVI	Bentazon (BTZ)	Wei et al. (2016)
11.	Graphene-coated nZVI nanocomposites (G-nZVI)	Trichloronitromethane (TCNM) anhalonitromethanes (HNMs); disinfectant by-product	Chen et al. (2016a)
12.	H_2O_2 and $KMnO_4$ modified ZVI	Nitrate	Guo et al. (2015a)
13.	Attapulgite, a magnesium aluminum phyllosilicate, supported nZVI	Nitrate-nitrogen contamination	Dong et al. (2018b)
14.	Porous titanium dioxide decorated nZVI (TiO_2@nZVI)	Hexavalent Cr(VI)	Petala et al. (2016)
15.	ZVI-activated persulfate (ZVI/PS)	BPA and phosphate	Zhao et al. (2016)
16.	Alginate and polyvinyl alcohol (PVA)-alginate entrapped nZVI	Cu(II), Cr(VI), Zn(II), and As(V)	Sun et al. (2018)
17.	Magnetite corn cob silica (MCCS) supported nZVI	Hexavalent Cr(VI)	Kumari et al. (2018)

In another study, iron supported nZVI on activated carbon (nZVI/AC) was reported to significantly enhance the pollutant entrapment efficiency. The researchers used 2:1 ratio of nZVI and AC along with thermal treatment of AC at 950 °C for 2 h for efficient removal of nitrate and phosphate in wastewater (Khalil et al. 2017). Yamaguchi et al. used ZVI/Cu bimetallic catalyst for significant removal of azo-dye orange II in wastewater treatment at pH 3 and 8 (Yamaguchi et al. 2018). They confirmed the role of Cu deposited ZVI in reductive degradation by energize hydrogen atom and e^- transfer instead of oxidative degradation by OH radical. Similarly, a strong oxidant, pederrsulfate modified ZVI (0.787 mM) was reported to decompose 0.021 mM bentazon (BTZ) in agriculture wastewater under standard ambient temperature and pressure (SATP, 298.15 K, and 100 kPa) (Wei et al. 2016). In the direction of drinking water purification, Chen et al. have used graphene-coated nZVI nanocomposites for water disinfection. They demonstrated small quantity, 60 mg/L, of G-nZVI composite degraded 99% trichloronitromethane (TCNM), anhalonitromethanes (HNMs); disinfectant by-product, via dechlorination and denitration within 120 min (Chen et al. 2016a). Similarly, common oxidants H_2O_2 and $KMnO_4$ modified ZVI surface was reported to reduce nitrate from contaminated groundwater (Guo et al. 2015a). The 94% and 97% nitrate degradations were observed at pH 5 with H_2O_2-ZVI and $KMnO_4$-ZVI, respectively, and 74% and 98% degradation at pH 7. Dong et al. utilized high surface area and excellent adsorption properties of attapulgite, a magnesium aluminum phyllosilicate, supported nZVI for nitrate-nitrogen removal from contaminated groundwater (Dong et al. 2018b).

Petala and team have developed magnetic photocatalytic material of porous titanium dioxide decorated nZVI for hexavalent Cr(VI) removal from wastewater under UV-C irradiation (Petala et al. 2016). They supported the strong magnetic photocatalytic property of TiO_2@nZVI nanocomposite matrix along with its reusability in wastewater treatment. Zhao and colleagues demonstrated ZVI-activated persulfate (ZVI/PS) induced strong oxidizing sulfate radicals ($SO_4^{\bullet-}$) production in the oxidation of BPA and phosphate in wastewater treatment (Zhao et al. 2016).

In continuation of advanced technique in wastewater treatment, Sun et al. have developed alginate and polyvinyl alcohol (PVA)-alginate entrapped nZVI for metalloids removal (Cu(II), Cr(VI), Zn(II) and As(V)) in saline wastewaters from hydraulic fracturing (Sun et al. 2018). They also demonstrated the mechanism of accelerated e^- transfer after the dissolution of non-conductive polymeric immobilization matrix to reduce Cu(II) and Cr(VI) in wastewater, although surface micropore blockage of nZVI-based system suppressed Zn(II) and As(V) removal. In direction of designing biodegradable composite supported nZVI-based system, Kumari and team have developed magnetite corn cob silica (MCCS) supported nZVI system captured hexavalent Cr(VI) in wastewater remediation (Kumari et al. 2018).

11.2.6 Nanowires and Nanofibers

The semiconducting nanofibers have substantial potential in water remediation processes remarkably in organic and biological pollutants degradation (Table 11.6). Mesoporous ZnO nanofibers mats were reported very effective in polycyclic aromatic hydrocarbons (PAH), anthracene and naphthalene photocatalytic degradation

Table 11.6 Nanowires and nanofibers for wastewater purification

S. no	Nanowires and nanofibers	Contamination	References
1.	Mesoporous ZnO nanofibers mats	Polycyclic aromatic hydrocarbons (PAH), anthracene and naphthalene	Singh et al. (2013a)
2.	Carbon nanofibers (CNFs)@I-doped $Bi_2O_2CO_3 - MoS_2$ membranes	RhB	Hu et al. (2018)
3.	Silver orthophosphate loaded inorganic hydroxyapatite (HAP) nanowires	*E. coli* and *S. aureus;* Pb(II) and dye, RhB	Li et al. (2015)
4.	Dithiocarbamate functionalized siliceous shells encapsulated magnetic nickel nanowires	Mercury ions	Pinheiro et al. (2014)
5.	Graphene-doped polyaniline coated TiO_2 nanoparticles and ZnO nanowires	Methyl orange	Gunti et al. (2017)
6.	MWCNTs/ultralong MnO_2 nanowires (UL-MnO_2-NWs)	Oil	Yue et al. (2018)
7.	Zirconia (ZrO_2) embedded carbon nanowires (ZCN)	As(III) and As(V)	Luo et al. (2016)
8.	Photocatalytic TiO_2 functionalized PEI membrane	RhB	Jiang et al. (2018)
9.	Single-crystalline $BiFeO_3$ (BFO) nanosheets and nanowires	Organic pollutant including RhB dye	Mushtaq et al. (2018)
10.	Bacteria generated amorphous twisted iron-oxide nanowires (ION)	Arsenic III and V	Andjelkovic et al. (2017)
11.	Cuprous oxide (Cu_2O) nanorods on phosphor-copper meshes	Oil	Kong et al. (2015)
12.	Ultralong hydroxyapatite (HAP) nanowires	Fluoride	He et al. (2016a)
13.	MnO_2 conjugated polyurethane (PU)	Edible oils, organic solvents or fuels	Zhang et al. (2017a)

(Singh et al. 2013a, b). Similarly, single-crystalline $BiFeO_3$ (BFO) nanosheets and nanowires were reported to enhance the piezoelectrical photocatalysis of organic pollutant including PhB dye (Mushtaq et al. 2018). The solar light and mechanical vibration were attributed to rapid and effective pollutant breakdown. Instead of high purification properties, photocatalytic ZnO and NiO nanofibers exhibited low surface area and rapid recombination rate of electrons and holes to block photocatalytic reactions (Malwal and Gopinath 2015). To overcome these issues, researchers developed doped and nanostructures composites in water remediation steps (Siriwong et al. 2012). Hu et al. demonstrated the photocatalytic property of carbon nanofibers (CNFs)@I-doped $Bi_2O_2CO_3$–MoS_2 membranes in water purification (Hu et al. 2018). Very small amount, 5 mg, of CNFs@I-doped $Bi_2O_2CO_3$–MoS_2 nanocomposite membrane exhibited photodegradation of 1×10^{-5}M RhB under visible light irradiation within 5 min.

The silver orthophosphate loaded inorganic hydroxyapatite (HAP) nanowires showed sublime photocatalytic activities and anti-bacterial capacities on *E. coli* and *S. aureus* along with higher adsorption of Pb(II) and dye, RhB from water samples (Li et al. 2015). Pinheiro et al. developed dithiocarbamate functionalized siliceous shells encapsulated magnetic nickel nanowires, and these nanosorbents were reported to remove ~99% mercury ions from 50μ/L aqueous solution in 24 h contact time (Pinheiro et al. 2014). In one study, graphene-doped polyaniline coated TiO_2 nanoparticles and ZnO nanowires demonstrated improved photoelectrochemical catalytic performance in the removal of methyl orange in water (Gunti et al. 2017). In another study, super-hydrophilic MWCNTs/ultralong MnO_2 nanowires (UL-MnO_2-NWs) were reported idle candidates for oily wastewater remediation along with its high reusability, high separation ability and high chemical stability under strong acidic/basic solutions of surfactant-stabilized oil-in-water emulsion (Yue et al. 2018). Luo et al. exhibited efficient adsorption property of zirconia (ZrO_2) embedded carbon nanowires (ZCN) in water purification (Luo et al. 2016). They used partial density of state (PDOS) analysis and Dubinin–Radushkevich (D-R) model calculations for the chemo-adsorption of As (III) and As(V)along with density functional theory (DFT) calculations for different configurations of the As compounds. Other than chemically synthesized nanowires, bacteria generated amorphous twisted iron-oxide nanowires (ION) demonstrated considerable adsorption capacity of arsenic III and V from groundwater remediation (Andjelkovic et al. 2017). Not restricted to pure chemical science, Jiang et al. used the flexible polymeric hybrid membrane of polyetherimide (PEI) and titania (TiO_2) nanowires for photocatalytic and ultrafiltration applications in water remediation (Jiang et al. 2018). The TiO_2 functionalized PEI membrane degrades RhB in water samples under UV light illumination along with its high hydrophilicity and permeability.

In a similar study, researchers used cuprous oxide (Cu_2O) nanorods on phosphor-copper meshes to remove offshore oil spill cleanup in short reaction time (Kong et al. 2015). Not restricted to this, ultralong hydroxyapatite (HAP) nanowires exhibited high fluoride adsorption capacity at very low fluoride concentration in water samples (He et al. 2016a, b). Similarly, Zhang and his colleagues utilized adsorption properties of MnO_2 and swelling property of polyurethane (PU) foam in the removal of edible oils, organic solvents or fuels from wastewater (Zhang et al. 2017a).

11.2.7 Magnetic Nanoparticles

Magnetic nanoparticles (MNP) were reported very powerful tool to filter microorganisms, toxic compounds and waste materials efficiently from drinking water (Table 11.7). The nanoporous/nanotunnel manganese oxides and hydrous manganese oxide (HMO) were reported to adsorb Pb (II), Cd (II) and Zn (II) and other divalent metals through external functionalization followed by intraparticle

Table 11.7 Magnetic nanoparticle-based water remediation

S. no.	Magnetic nanomaterials	Contamination	References
1.	Nanoporous/nanotunnel manganese oxides and hydrous manganese oxide (HMO)	Pb(II), Cd(II) and Zn (II) and other divalent metals	Gupta et al. (2015), Anjum et al. (2016)
2.	3-aminopropyltrimethoxysilane modified Fe_2O_3 nanoparticles	Cr^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Cd^{2+}, Pb^{2+} arsenic and fluoride	Palimi et al. (2014), Gupta et al. (2015)
3.	1-D CNT on graphene decorated iron nanoparticles	Microorganisms	Sharma et al. (2015)
4.	Fe_3O_4 modified graphene (G) and inorganic–organic sol-gel hybrid (TEOS-MTMOS)	Organophosphorus pesticides (OPP)	Rashidi Nodeh et al. (2017)
5.	F-N co-doped $TiO_2/C/ZnFe_2O_4$ (ZCT-FN) magnetic photocatalyst	–	Wei et al. (2018)
6.	Ferrite magnetic nanoparticles $Co_{0.5}Zn_{0.25}M_{0.25}Fe_2O_4$ (M = Ni, Cu, Mn, Mg) (MNPs) along with TiO_2	Methyl orange and methylene blue	Ciocarlan et al. (2018)
7.	Maghemite (γ-Fe_2O_3)	Pb^{2+} and Cu^{2+}	Rajput et al. (2017)
8.	Polypyrrole functionalized arginine and Fe_3O_4 nanocomposites (magnetic arginine), Fe_3O_4@Arg-PPy	Cr(IV)	Chigondo et al. (2018)
9.	Chitin-coated MWCNTs decorated magnetite	Cr(IV)	Salam (2017)
10.	Polyethylenimine (PEI) functionalized magnetic ceramsite (MC) coated by nano carbon spheres (MCCS)	Cr(IV)	Zhou et al. (2018)

diffusion in inner sphere via ion exchange process (Gupta et al. 2015; Anjum et al. 2016). In other cases, hierarchical ZnO nanorods are widely used for heavy metal removal from wastewater. The ZnO nanosheets, nanoplates and nano-assemblies showed high removal efficiency of Co^{2+}, Ni^{2+}, Cu^{2+}, Cd^{2+}, Pb^{2+}, Hg^{2+} and As^{2+} due to their unique structure and electropositive nature (Singh et al. 2013a; Gupta et al. 2015). Similarly, MgO microsphere, nanorods, nanowires and other 3-D entities were reported efficient adsorption of Pb^{2+} and Cd^{2+} from industrial wastewater (Engates and Shipley 2011; Gupta et al. 2015; Anjum et al. 2016).

The natural occurrence of iron and easy synthesis method of iron oxides at very low cost makes it a very common chemical in water purification method. The 3-aminopropyltrimethoxysilane and other surface modification of Fe_2O_3 nanoparticles were reported to remove several heavy materials like Cr^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Cd^{2+}, Pb^{2+} arsenic and fluoride from water (Palimi et al. 2014; Gupta et al. 2015). The 2-D structure and high surface to volume ration of graphene make them valuable in wastewater treatment. Sharma et al. have enhanced adsorbent and anti-bacterial property of 1-D CNT on graphene via decorating the nanocomposite with iron oxide to procure the 3-D structure of the whole composite (Sharma et al. 2015). Rashidi Nodeh and colleagues also developed Fe_3O_4 modified with graphene (G) and inorganic–organic sol-gel hybrid (TEOS-MTMOS) as an adsorbent for organophosphorus pesticides (OPP) in water samples (Rashidi Nodeh et al. 2017). In direction of the photocatalytic property of magnetic nanocomposites, their use was increased abundantly used in water remediation. The F–N co-doped TiO_2/C/$ZnFe_2O_4$ (ZCT-FN) magnetic photocatalyst was reported to use in wastewater treatment under UV light irradiation (Wei et al. 2018). In continuation of water remediation, co-precipitated ferrite magnetic nanoparticles $Co_{0.5}Zn_{0.25}M_{0.25}Fe_2O_4$ (M = Ni, Cu, Mn, Mg) (MNPs) along with TiO_2 degraded methyl orange and methylene blue in solar light range (Ciocarlan et al. 2018). Another superparamagnetic nanomaterial of maghemite (γ-Fe_2O_3) was reported to adsorb Pb^{2+} and Cu^{2+}at pH $\sim$ 5.0 of the water (Rajput et al. 2017). Similarly, polypyrrole functionalized arginine and Fe_3O_4 nanocomposites (magnetic arginine), Fe_3O_4@Arg-PPy, was also reported to adsorb toxic Cr(IV) from wastewater sample with 65% adsorption efficiency retention (Chigondo et al. 2018).

Salam developed chitin-coated MWCNTs along with magnetite and high adsorption property of MWCNT adsorb Cr(IV) from water samples (Salam 2017). This complete process of Cr(IV) removal was carried out thermodynamically and kinetically. In another study, Zhou et al. used polyethylenimine (PEI) functionalized magnetic ceramsite (MC) coated by nano carbon spheres (MCCS) in the removal of metallic contamination from drinking water (Zhou et al. 2018). This MCCS nanocomposite exhibited high adsorption capacity for Cr(IV) due to its high porosity and superabundant functionalized group along with its strong electrostatic bonds.

11.3 Commercially Available Technique

The company NanoH_2O (Los Angeles, CA, USA) developed and introduced the QuantumFlux membrane to the market for liquid application (reverse osmosis), which can be classified as a mixed matrix membrane (WO 2006/098872 A3). This membrane was generated by adding super-hydrophilic nanoparticles to a polyamide thin film to form a thin film nanocomposite membrane with higher permeate efficiency and lower fouling potential. The nanoparticles are designed to attract water and are highly porous, soaking up water like a sponge while repelling dissolved salts and other impurities. The hydrophilic nanoparticles embedded in the membrane also repel organic compounds and bacteria, which tend to clog up conventional membranes over time (Gehrke et al. 2015).

One already patented nanofiber filter is NanoCeram® (Argonide Corporation, Sanford, FL, USA), an electropositive filter medium that is implemented in a filter cartridge. NanoCeram is a small diameter fiber, with a high surface area (300–600 m^2/g), that can be produced in kilogram quantities by a proprietary sol-gel reaction. The product is a white, free-flowing powder consisting of fibers approximately 2 nm in diameter and tens to hundreds of nanometers in length that collects in aggregates. Embedded into a glass and cellulose nonwoven sheets, a filtration material is created that is comparable with ultrafiltration but has higher flow rates that attract dirt, bacteria, viruses and proteins using an electrostatic effect (Gehrke et al. 2015).

An excellent model system based on bionanocomposites has been also presented by a team from India (http://www.scientificamerican.com/article/cheap-nanotech-filter-water/). They developed a portable twofold system of separate components for microbes (the upper filter unit and microbial membrane), and a multilayer filter block, which can be customized in dependence on the occurring contaminants. The microbe filter is built of silver nanoparticles embedded in aluminum hydroxide nanoparticles/chitosan composite, designed in a way to block the macroscale water contaminants and protect the nanoparticles from the contaminants, which otherwise would accumulate on their surfaces, thus reducing their microbe-killing power. The membrane filter at the top kills a variety of microorganisms, and the multilayered filter block at the bottom can be custom-fitted for lead, mercury or arsenic.

The last example that gained a lot of attention is a cheap, bionanocomposite-based filter prototype developed by researchers at the Lulea University of Technology (Sweden) in collaboration with the Imperial College (UK) (http://www.nanowerk.com/nanotechnology-news/newsid=38556.php). They have combined a cheap residue from the cellulose industry, with functional nano-cellulose to prepare adsorbent sheets with high filtration capacity toward environmentally hazardous contaminants from industrial effluents (heavy metal ions from industrial waters, dyes residues from the printing industry and nitrates from municipal water).

11.4 Risks and Limitations

Although nanotechnology-based methods offer a rapid, advanced and broad range of potential uses in water remediation techniques, this may also have unintended adverse effects on human health and environment. The water remediation techniques involve artificially synthesized and metallic nanoparticles and its oxides which are non-biodegradable and very harmful to some extent. The toxicological concerns of nanomaterials are exacerbated by the poor knowledge and understanding of nanoparticles behavior on human and environment. Therefore, nanoparticle properties toward its applications, their toxicity tests (both nanotoxicity and ecotoxicity) and technology assessment need to be carried out for the use of nano-based materials and processes for water remediation. Currently, many studies yielded contradictory outcomes since no universal standards and regulations have been defined which directly affects the necessary procedure to be followed in water remediation.

In order to combine water and nanotechnology, there are joint calls for "low-energy solutions for drinking water production" that involve implementation of novel nano-engineered materials and processes for water applications. The European Water Framework Directive and REACH63 (Registration, Evaluation, Authorization and Restriction of Chemicals) also initiated a safety evaluation of nanomaterials in water derivatives (Gehrke et al. 2015). Similarly, the Environmental Protection Agency, USA, has permitted limited manufacture of new nanomaterial entity under Toxic Substances Control Act, but still no regulation on nanotechnology-based water remediation techniques was mentioned (US Environmental Protection Agency). Without any standard rules and regulations' extensive use of nanomaterials in water treatment, toxicity studies are very essential to carry out in this area. Although TiO_2 is most commonly used in water remediation, US Environmental Protection Agency in 2010 has reported miscellaneous effects of the compound on water sources and microorganisms present in it (European Protection Agency 2010); therefore, use of TiO_2 in water treatment is questionable. However, there are still several drawbacks that must be negotiated. Materials functionalized with nanoparticles incorporated or deposited on their surface have risk potential, since nanoparticles might release and emit to the environment where they can accumulate for long periods of time. Up until now, no online monitoring systems exist that provide reliable real-time measurement data on the quality and quantity of nanoparticles present only in trace amounts in water, thus offering a high innovation potential. Another more technical limitation of nano-engineered water technologies is that they are rarely adaptable to mass processes, and at present, in many cases are not competitive with conventional treatment technologies.

11.5 Conclusion and Future Prospects

There is a significant need for novel advanced water technologies, to ensure a high quality of drinking water, eliminate micropollutants and intensify industrial production processes using flexibly adjustable water treatment systems. Nano-engineered materials, such as nano adsorbents, nanometals, nanomembranes and photocatalysts, offer the potential for novel water technologies that can be easily adapted to customer-specific applications. Most of them are compatible with existing treatment technologies and can be integrated simply in conventional modules. One of the most important advantages of nanomaterials when compared with conventional water technologies is their ability to integrate various properties, resulting in multifunctional systems such as nanocomposite membranes that enable both particle retention and elimination of contaminants. Further, nanomaterials enable higher process efficiency due to their unique characteristics, such as a high reaction rate. This chapter has summarized the current state of play for research into nanocomposites for water treatment. This field of research is swiftly developing, with some "nano" products already seeing the commercial application. Still, to date, no magic bullet nanocomposite has yet emerged commercially. The key challenge lies in successfully increasing the surface area of reactive material without sacrificing the mechanical properties to an inoperable level while also keeping costs to a minimum. Continued development is still needed to advance such materials, with further investigations into substrates, anchoring/impregnating methods and post-synthesis treatments that may improve the nano-reactivity. Furthermore, standardized tests should be implemented by the academic community to allow for performance comparisons to be made between materials, thereby making it easier for investors to champion-specific and promising materials for further development. Given the present speed of technological development and market uptake, the future looks extremely promising for nanocomposites, not only for water treatment, but for many other important global industries.

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Chapter 12
Applications of Algal Nanoparticles in Agriculture

Monika Joshi, Rupal Sarup, Kannikka Behl, Mahima Sharma and Subhasha Nigam

Abstract Agriculture is considered as a backbone for most of the developing countries around the world. Since the population is continuously increasing, it is necessary to use modern technologies of nano- and biotechnology in agricultural sciences. Nano-biotechnology offers solution in all stages of growth, processing, production, storing, packaging and transportation of agricultural products. Nano-biotechnology can revolutionize both food and agroindustries by proving better crop protection against several diseases, better shelf life, enhanced yield, more nutritional value and better resistance to harsh environmental conditions. Nanoparticles can now be easily synthesized via biological routes and can be instantly applied for agricultural purposes. Algae (macro/micro) are leading front runner in producing nanoparticles that can successfully provide several versatile applications. Algae play an important role in agriculture. Seaweeds (macroalgae) are used as fertilizers, resulting in less nitrogen and phosphorous run-off than the one from the use of livestock manure. This chapter provides an insight on various species of algae that can be used in nanoparticle synthesis and the advantages it can provide in agricultural activities.

Keywords Algae · Nano-biofertilizers · Biosynthesis · Nanoparticles · Nanofungicides · Nanocomposite

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12.1 Introduction

Algae are a group of organisms that are capable of photosynthesis. They are autotrophic, thalloid plants but lack true root, stems and leaves. Based on the characteristics, the term “algae” includes the prokaryotic organisms which are called “cyanobacteria” and eukaryotic organisms which are called “algae” (Sheath and Wehr 2015). Algae are available universally in different kinds of habitats of which aquatic habitat is the most common one. On the basis of the habitat, algae can be divided into three major groups which include aquatic algae (algae which are present in freshwater or saline water), terrestrial algae (which can be present on the surface of soil which are called as *Saprophytes* or can be present under the surface of soil which are called as *Cryptophytes*) and unusual habitats which include halophytic, epiphytic, epizoic, endozoic, cryophytic, lithophytic and parasitic algae (Dodds and Whiles 2010; Wehr and Sheath 2015). They occur in a variety of habitats, but most of them are aquatic and show alternation of generation. Based on the colour, algae can be divided into four major groups that include (Baweja and Sahoo 2015; Vashistha et al. 2010):

- *Cyanophyceae or Myxophyceae* These include blue–green algae which have c-phycocyanin as the dominant pigment.
- *Chlorophyceae* These include green algae which have chlorophyll a and b as dominant pigments.
- *Phaeophyceae* These include brown algae which have fucoxanthin as its dominant pigment.
- *Rhodophyceae* These include red algae which have R-phycoerythrin as its dominant pigment.

Algae can undergo reproduction by asexual, vegetative as well as sexual means (Raven and Giordano 2014). The vegetative means of reproduction followed by algae include fragmentation, hormogonia formation, formation of adventitious branches, tubers and budding (Arora and Sahoo 2015; Ngan and Price 1980). Algae can also undergo asexual reproduction by the means of asexual spores like zoospores, aplanospores, hypnospores, tetraspores, autospores, exospores and endospores (Arora and Sahoo 2015; Bullock 1978; Ott et al. 2015). The sexual means of reproduction of algae include hologamy, autogamy, isogamy, anisogamy and oogamy (Arora and Sahoo 2015; Campbell 1990).

Algae are one of the emerging sustainable resources for food, fuel, feed and many other products (Khan et al. 2017b). Nowadays, algae are used in various fields because the growth rate of algae which is very fast (Khan et al. 2018). It can double its number in very few hours, and it can consume carbon dioxide which is generated by power plants. Algae can be grown in sea and even on land; they can purify wastewaters and are also able to produce various products like lubricants, plastics, fertilizers and cosmetics (Khan et al. 2018; Lu et al. 2018). The use of algae in agriculture is increasing day by day. There are various applications of algae as shown in Fig. 12.1. These include nitrogen fixation, uptake of phosphorus,

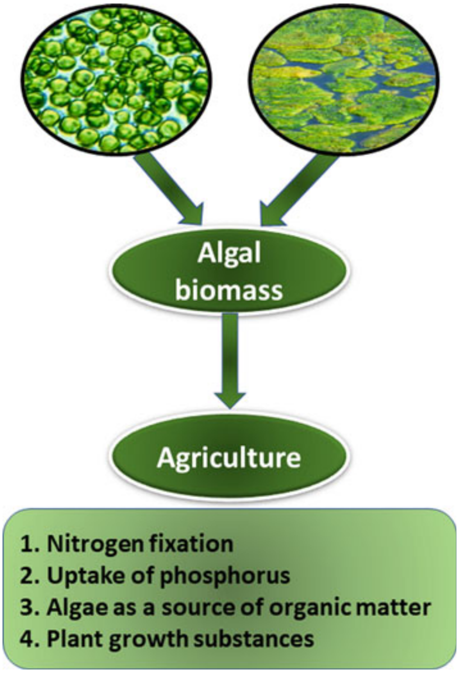

Fig. 12.1 Schematic representation of algal biomass in agriculture

as a source of organic matter, plant growth substances, which are reviewed in another chapter of this book (Chap. 25).

However, there are some limitations in usage of algae in agriculture, like some of the blue–green algae and *Spirulina* can be harmful to the health of human beings as they contain various toxins like neurotoxins (Deng and Chow 2010; Roy-Lachapelle et al. 2017). If the blue–green algae contaminate food, then it can cause nausea, liver damage, stomach pain, shock and even death (Nicoletti 2016). Some microalga may contain iodide and so it can act as allergen to people who are sensitive to iodine (Nicoletti 2016). Some people can be allergic to algae, and its symptoms include difficulty in breathing, swelling and rash (Willis et al. 2018). Some of the algae are rich in sodium, so it cannot be preferred by the people who have high blood pressure (Jha et al. 2017). The people who are suffering from phenylketonuria should not take in *Spirulina* as they can react with the medications, thereby suppressing the immune functions (Deng and Chow 2010; Udayan et al. 2017).

To overcome the above limitations, nowadays nanoparticles are being used in various fields as they act as a bridge between the molecular or atomic structures and the materials in bulk (Xu et al. 2009). The engineered nanoparticles have various properties which make them different from the molecular as well as bulk materials (Prasad et al. 2017). Some of these properties are enhanced reactivity, eco-friendly, non-toxic, surface area is small, and its surface structure is atypical (Prasad et al. 2017). The properties of the nanoparticles listed above are mainly due to shape, stability, chemical composition and surface structure of the nanoparticles

(Kim et al. 2018). These nanoparticles can be synthesized by various ways which include chemical and biological methods (Rai and Ingle 2012). Chemical methods used for the synthesis of nanoparticles are not performed as certain toxic chemicals can get absorbed on the surface of these nanoparticles making them unsuitable for biological application (Ghormade et al. 2011; Rai and Ingle 2012; Servin and White 2016). Certain other eco-friendly methods are preferred for the synthesis of nanoparticles which include the use of microorganisms, algae, fungus, enzymes and plant extracts (Kashyap et al. 2015; Parisi et al. 2015).

12.2 Application of Nanotechnology in Agriculture

The application of nanotechnology in plant producing systems and plant sciences is called phyto-nanotechnology. This technology helps in the production of "smart" crops, because the nanomaterials help in providing programmed multifunctional, time-controlled and self-regulated capabilities (Prasad et al. 2017; Servin and White 2016). Nanotechnology-based research and development is likely to facilitate and frame the next stage of animal production inputs, development of genetically modified crops, chemical pesticides and precision farming techniques.

12.2.1 Nanoparticles for Targeted and Controlled Release of Agrochemicals

As reviewed by other authors in this book, the engineered nanoparticles can deliver various agrochemicals like herbicides, fertilizers and pesticides which can be done to meet the nutritional requirements of the plant and also to protect it from any kind of pathogen or pest attack (Khot et al. 2012). It is because of these nanoparticles, the repeated application of harmful pesticides and fertilizers can be reduced (Rai and Ingle 2012). Some of the nanoparticles are also being designed in a manner to protect the agrochemicals present in it from degradation (Chen and Yada 2011; Huang et al. 2018). Special nanoparticle-based fertilizers, known as nano-fertilizers, are also used which help in increasing the efficiency of the plant to use the nutrients present in the soil (Ghormade et al. 2011).

12.2.2 Nanoparticles as Vehicles of Delivery of Various Bioactive Molecules

Engineered nanoparticles can also be used to deliver various molecules like proteins, nucleotides, DNA and activators through the plant cells that have been isolated to transfer the characters of interest (Riley and Vermerris 2017). Certain proteins as well as enzymes can also be delivered to the plants which are useful in biochemical analysis or any modification that needs to take place at gene level (Torney et al. 2007).

12.2.3 Translocation of Nanoparticles in Plants

Some studies have indicated that uptake of nanoparticles can take place in the plants directly (Gogos et al. 2016; Pérez-de-Luque 2017; Rico et al. 2011). The nanoparticles which were used in these studies include silica nanoparticles, gold nanoparticles, zinc oxide nanoparticles and copper oxide nanoparticles (Aslani et al. 2014; Rajput et al. 2018). In an experiment, it has been shown that magnetic Fe_3O_4 nanoparticles (0.5 g/L) were translocated directly in the plant of pumpkin (*Cucurbita maxima*) leading to enhanced production with no toxic effect to the plant (Wang et al. 2011).

12.2.4 Nanocomposite

As the nanoparticles are added to the matrix to form the nanocomposite, its properties get improved. The improved properties include thermal and electric conductivity, toughness and mechanical strength, decrease water, gas and hydrocarbon permeability, thermal stability and chemical resistance (Wen et al. 2017). These nanocomposites are used in various fields including agriculture (Servin and White 2016). They are used for storage of energy, treatment of water, detection of pests and their control as well as to increase the productivity of the agricultural land and enhancing its nutrients' uptake (Khot et al. 2012). Nanocomposites are mainly used in agriculture due to their applications in pest management in plants and plant growth (Singh et al. 2015). *Stauroneis* sp. which are diatoms are used for the formation of silicon–germanium nanocomposites (Asmathunisha and Kathiresan 2013). This type of formation of nanocomposites has great importance in various fields because of its effectiveness, accessibility and simplicity (Asmathunisha and Kathiresan 2013; Khot et al. 2012). The major use of nanocomposites is for the removal and management of plant pests (Rai and Ingle 2012). They have antibacterial effects which help in decreasing the number of bacteria which affect the plants. These nanocomposites act by disrupting the cell membrane of the bacteria, introducing certain antibacterial effects by the interactions with DNA and proteins (Chen and Yada 2011). The actual mechanisms by which these nanocomposites act are still not known, but its use and importance will increase in the future due to its various advantages.

12.3 Application of Nanotechnology Combined with Algae in Agriculture

The successful application of various algae-mediated nanomaterials has generated interest in agri-nanotechnology. These algal-mediated nanomaterials hold the promise of controlled release of agrochemicals, site-targeted delivery of various macromolecules needed for enhanced plant growth and efficient nutrient utilization. These nanomaterials have applications such as nano-fertilizers, nano-biofertilizers, nano-pesticides and nano-biosensors and are discussed below.

12.3.1 Nano-biofertilizers

Nano-biofertilizers are formed from three words "nano", "bio" and "fertilizers". The word "nano" means nanomaterials which are materials whose size range from 1 nm to 100 nm. The word "bio" means that it is living or is made up of certain living organisms and "fertilizers" are materials which provide the soil as well as plant tissues with suitable nutrients (Duhan et al. 2017). Thus, nano-biofertilizers are nanomaterials formed from beneficial organisms such as *Rhizobium*, blue–green algae, mycorrhiza which supply nutrients to plants for increased growth rate and yield (Duhan et al. 2017). Nano-fertilizers can be divided into two categories: macronutrient nano-fertilizers and micronutrient nano-fertilizers (Liu and Lal 2015). Microorganisms used for formation of nanoparticles convert the organic matter present in soil to simpler substances, thereby improving fertility and providing essential nutrients. A major drawback of using biofertilizers is the availability of a shorter shelf life and desiccation, thereby leading to various problems (Guo et al. 2018). So, to overcome this problem, nano-biofertilizers are used in which the water around the microorganisms is entrapped by the oil. This technique is known as water-in-oil emulsion (Malusá et al. 2012). This helps in preventing desiccation as well as increasing the viability of cells. Hydrophobic silica particles are good nanoparticles as they increase the cell viability as it thickens the oil phase during storage (Duhan et al. 2017). Blue–green algae such as *Anabaena* sp., *Nostoc* sp. *and Aulosira* sp. can fix atmospheric nitrogen and can be used as a biofertilizer in paddy fields (Khan et al. 2017a). These algae along with nanoparticles need to be evaluated in field condition for their impact on the growth promotion of plants. As in one study, it was found that the combination of nano-zinc chelate with biofertilizers has positively impacted the yield components of maize crop under water stress condition (Farnia and Omidi 2015).

12.3.2 Synthesis of Nanoparticles Using Algae

(a) Silver nanoparticles: Silver nanoparticles have reported applications in various fields like antifungal and antimicrobial activities (Kathiraven et al. 2015; Salari et al. 2016). Various classes of algae are used for the synthesis of silver nanoparticles like cyanobacteria, macroalgae and microalgae (Salari et al. 2016; San Keskin et al. 2016; Soleimani and Habibi-Pirkoohi 2017). The results of the studies are discussed further.

Cyanobacteria: Octahedral and spherical silver nanoparticles have been synthesized using a filamentous cyanobacteria *Plectonema boryanum UTEX 485* (Thakkar et al. 2010). The intracellularly synthesized nanoparticles were 10 nm in size, and those which were synthesized extracellularly had a size which varied from 1 to 200 nm. *Oscillatoria willie NTDM01* has also formed silver nanoparticles, with the size ranging from 100 to 200 nm by the extracellular method (Ali et al. 2011). *Spirulina plantensis* has also been used to synthesize silver nanoparticles. The size, the shape and the number of synthesized nanoparticles were dependent on the time period of exposure and concentration of silver ions (Sharma et al. 2015). Other cyanobacterial species like *Cylindrospermum, Microcheate, Lyngbya, Anabaena,* etc., have also been used for the silver nanoparticles' synthesis (Husain et al. 2015).

Microalgae: *Chlorella vulgaris,* a green microalga, has been used to synthesize appreciable yield of silver nanoparticles (Soleimani and Habibi-Pirkoohi 2017). *Nannochloropsis oculata* and *C. vulgaris* have synthesized silver nanoparticles with the size less than 15 nm (Mohseniazar et al. 2011). *Chlorella pyrenoidosa* has also synthesized spherical silver nanoparticles with the size ranging from 5 to 10 nm (Elumalai et al. 2013). *Chlamydomonas reinhardtii* has also been used to synthesize rectangular and round silver nanoparticles under both in vitro and in vivo conditions (Ahmadi et al. 2016).

Macroalgae: Silver nanoparticles have been prepared easily using brown and red macroalgae (Abdel-Raouf et al. 2018). Green algae *Ulva fasciata* have been used for preparation of silver nanoparticles which are 40.5 nm in size and spherical in shape (Hamouda et al. 2018a, b). *Codium capitatum* has been used for the synthesis of silver nanoparticles (Kannan et al. 2013). The size of these nanoparticles ranges from 3 to 4.4 nm and have a mean size of 30 nm (Kannan et al. 2013). The amines, sulphate groups and peptides present in these nanoparticles are involved in the reduction process and thus can stabilize the silver nanoparticles. A brown alga, *Padina pavonica,* was also used for the synthesis of silver nanoparticles whose size ranges from 45 to 64 nm (Abdel-Raouf et al. 2018). These nanoparticles were very effective in agriculture as they showed antibacterial activity against *X. campestris* and *Fusarium oxysporum* which are said to be the cotton pathogens and can cause diseases in its plants.

(b) Synthesis of gold nanoparticles using algae: Gold nanoparticles are used nowadays in various fields because of the ease by which they can be prepared and because of their non-toxic nature. Gold nanoparticles can be prepared from various types of algae which include:

Cyanobacteria: Some cyanobacteria such as *Plectonema boryanum* have been reported for their ability to produce gold nanoparticles (Lengke et al. 2006). *Lyngbya majuscula* has been used for synthesis of both gold and silver nanoparticles (Bakir et al. 2018). This cyanobacterium was also able to produce gold nanoparticles that were 41 nm in size and had antibacterial activities against *S. aureus* and *B. Subtilis*. Gold nanoparticles have also been synthesized from *Synechocystis* sp. (Monica et al. 2011). Other cyanobacterial species such as *Phormidium tenue, Phormidium valderianum* and *Microcoleus chthonoplastes* have also been utilized in production of gold nanoparticles (Patel et al. 2015).

Microalgae: Many microalgae as well as diatoms are used for the synthesis of gold nanoparticles (Parial et al. 2012). Green algae *Chlorella vulgaris* have been used for the synthesis of certain hexagonal and triangular gold nanoparticles (Annamalai and Nallamuthu 2015). Microalgal species *Klebsormidium flaccidum and Tetraselmis kochinensis* have synthesized gold nanoparticles 15–20 nm in size (Dahoumane et al. 2012). A nanoparticle containing metals both gold and silver was used to synthesize nanoparticles using *C. Reinhardtii* (Bimetallic nanoparticles) (Rao and Gautam 2014). *Navicula atomus* and *Diadesmis gallica* have synthesized gold nanoparticles 9–22 nm in size (Schröfel et al. 2011).

Macroalgae: Different species of green algae, brown algae and red algae had been used for the synthesis of gold nanoparticles (Hassaan and Hosny 2018). Green algae *Ulva intestinalis*, *Rhizoclonium fontinales* and *Sargassum muticum* can synthesize gold nanoparticles intracellularly (Namvar et al. 2015; Parial et al. 2012).

(c) Synthesis of ZnO nanoparticles using algae: The use of zinc oxide nanoparticles (ZnO-NPs) has increased in various fields these days. These are involved in wastewater treatment, environmental remediation, pigments, cosmetics, bioimaging, electronic equipment and drug delivery systems (Mishra et al. 2017; Ong et al. 2018). The procedure that was initially used for preparing these nanoparticles increased toxicity as many different chemical reagents were used, so the procedure for preparation was shifted to green methods. In these methods, nanoparticles were synthesized using components of plants, marine algae (Sanaeimehr et al. 2018) and seaweeds (Ishwarya et al. 2018). One of the marine algae used for the synthesis of ZnO-NPs was *Sargassum muticum* (Azizi et al. 2014), and one of the seaweeds utilized was *Ulva lactuna* (Ishwarya et al. 2018). For preparing the *S. muticum* ZnO-NPs, the dry powder of marine algae was mixed with distilled water followed by heating and filtering. This algal extract was then mixed with zinc acetate di-hydrate solution followed by mixing, heating and washing leading to the formation of these nanoparticles (Azizi et al. 2014). Similarly, *Ulva lactuna* ZnO-NPs were also prepared. In this procedure, the seaweed extract was formed by mixing the dry weight of the seaweed with distilled water followed by boiling and filtering. This extract was then mixed with zinc acetate followed by heating and washing which lead to the formation of *Ulva lactuna* ZnO-NPs (Ishwarya et al. 2018). The *Sargassum muticum*-derived ZnO-NPs had shown properties like anticancer and anti-inflammatory

(Sanaeimehr et al. 2018). *Ulva lactuna*-derived zinc oxide nanoparticles had bactericidal activity and also acted as mosquito larvicides (Ishwarya et al. 2018).

12.3.3 Use of Nanoparticles Synthesised by Using Algae as Nanofungicides

The nanoparticles which are synthesized using algae can also act as an effective antifungal agent (El-Sheekh and El-Kassas 2016; Singh et al. 2015). Fusarium wilt is a kind of disease caused in plants due to the infection by the fungus *Fusarium oxysporum*. This fungus mainly attacks tomato, pepper, potato and egg plants. It normally enters the plants through the roots and affects the xylem which is the tissue present in the plants which is responsible for water transport (Kapoor 1988). As this fungal infection spreads into different parts like its stem and leaves, it restricts the transport of water in those parts of plants, thereby making the leaves to wilt and the colour of the leaves turning to yellow (Nirmaladevi et al. 2016). This infection increases from time to time, thereby infecting the new leaves also and eventually as this infection increases the plant also dies. This type of fungal disease normally develops when the temperature is high about 80 °F as well as when the moisture in soil is low and the weather is dry (Kapoor 1988). To prevent such kinds of fungal infections in plants, algal-mediated nanoparticles are used. The algae mainly used for the protection of plants from this fungal infection are *Sargassum longifolium,* and the nanoparticles are silver nanoparticles (Shofia et al. 2018).

12.3.4 Use of Nanoparticles Synthesised by Using Algae for Biosensing

To maximize the high production from agriculture with the minimum resources such as water, soil and fertilizer, the monitoring of the agriculture land and environment is necessary. The use of nano-biosensing is increasing nowadays in various fields like agriculture, environmental monitoring, health care, genome analysis, etc. (Prasad et al. 2017; Singh et al. 2015, 2016). A nano-biosensor is a biosensor converted into a compact analytical device containing a biological element joined with a physicochemical transducer (Malik et al. 2013). There are various ways by which these nano-biosensors are used in the field of agriculture (Antonacci et al. 2018; Mufamadi and Sekhejane 2017; Srivastava et al. 2018). Due to improper knowledge, sometimes the farmers use excess amount of nitrogen-rich fertilizer to their crops. Unfortunately, excess use of this fertilizer produces the biotoxins which take oxygen form the water and block the sunlight which in turn spoils the farming. The use of biosensor can monitor the nitrogen content of the soil (Abdel-Raouf et al. 2012). Apart from that, biosensor can monitor the large variety of insecticide, pathogens, pesticide, fertilizers, herbicide, pH, microbial load, quality of the soil and humidity by which they act as a useful tool to increase the productivity of that land (Singh 2017). They help in determining the quality of soil and are also used to diagnose whether any disease is present or not. They also act as agents which help in promoting sustainable agriculture with the help of nano-fertilizers (Singh 2017). Nanosensors and nano-based smart delivery systems are used for the detection of agricultural natural resources, e.g. H_2O, nutrients and chemicals through precision farming. They can also detect whether any type of contaminant or other molecules are present in the soil or not. Nowadays, they are also used for the analyses of different food products like for the detection of vitamins, antibiotics and food spoilage (Devi Lamabam and Thangjam 2016). Various single-celled organisms like different microalgae are used for the formation of nano-biosensors. These microalgae are preferred over other organisms as they can respond quickly to the changes that happen in their habitat because of their intracellular metabolic processes which takes place at a very high rate and because of their small size (Ferro et al. 2012; Naessens and Tran-Minh 1999; Turdean 2011). Synthesis and application of algal-mediated nanoparticles in agriculture are presented in Table 12.1.

12.4 Conclusion and Prospects

Even though phyto-nanotechnology is still a developing technology, it can create (a) new tools to deliver certain bioactive compounds leading to better plant growth, (b) smart agrochemical delivery systems and (c) novel routes for intracellular and extracellular imaging and labelling. Nanoparticles can now be easily synthesized via biological routes and can be instantly applied for agricultural purposes. Among the biological sources, algae (macro/micro) are leading front runner in producing nanoparticles that can successfully provide several versatile applications. The utilization of algae in the NPs' synthesis has encouraged the designing of green, simple, cost- and time-effective approaches through minimizing the use of solvents and synthetic chemicals. This green route of nanoparticle synthesis can be easily performed, even at room temperature, and is environmentally friendly. These nanoparticles provide an efficient resistance to diseases by plants and enhanced growth. Thus, nanotechnology gives a green, proficient and eco-friendly solution to pest and insect control, a growing concern in agriculture. The propelled nanotechnological devices and strategies can enhance the way agriculture is seen. Nanoparticles have an extraordinary potential as "magical projectiles" stacked with herbicides, fungicides, supplements, composts or nucleic acids that can focus on plant tissues to discharge their charge to accomplish the coveted outcomes. Biotechnological progressions and the availability of quick and exact diagnostic apparatuses combined with the power of nanoparticles can have an incredible and promising future for the cutting-edge horticulture activities

Table 12.1 Synthesis and application of algal-mediated nanoparticles in agriculture

Nanoparticles	Name of algae	Usage	References
Silver nanoparticles	*Spirulina plantensis*	Antibacterial agent	Muthusamy et al. (2017)
	Chlorella vulgaris	Antibacterial agent	Sharma et al. (2009)
	Padina boergesenii	Nanofungicides	Sahayaraj et al. (2011)
	Amphiroa anceps	Nano-biofertilizer	Roy and Anantharaman (2018a)
	Sargassum ilicifolium	Nano-biofertilizer	Roy and Anantharaman (2018b)
	Chaetomorpha antennina	Seed germination, antibacterial activity and nano-biofertilizer	Roy and Anantharaman, (2017)
	Ulva fasciata	Antibacterial agent	Hamouda et al. (2018a)
Gold nanoparticles	*P. boryanum UTEX 485*	Antibacterial agent	Lengke et al. (2006)
	Klebsormidium flaccidum	Antibacterial agent	Dahoumane et al. (2012)
	Ulva intestinalis	Antibacterial agent	Parial et al. (2012)
	Hypnea musciformis	Nanofungicides	Murugesan et al. (2015)
	Galaxaura elongata	Antibacterial agent	Abdel-Raouf et al. (2017)
ZnO nanoparticles	*Sargassum muticum*	Anticancer, anti-inflammatory, antioxidant, antidiabetic and anti-allergic	Sanaeimehr et al. (2018)
	Ulva lactuna	Bactericidal activity, mosquito larvicide	Ishwarya et al. (2018)

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Chapter 13
Structural and Ultrastructural Changes in Nanoparticle Exposed Plants

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Abstract The applications of nanoparticles on aquatic and terrestrial ecosystems are increasing and receiving a great scientific attention due to its toxicity effects. The phytotoxicity of nanoparticles is mainly expressed by suppressed germination percentage, impact on morphometric parameters, for instance, root and shoot length, root hairs, biomass, bio-molecules, and cellular damages such as lipid peroxidation, protein damage, membrane destruction, chlorophyll fluorescent, transpiration rate, and photosynthesis. Recent studies indicate several changes in plant cell organelles such as a disruption in the cell wall, cell membrane, chloroplast structure, thylakoids, abnormal size of plastoglobules and starch granules, destructive changes in peroxisomes, swollen mitochondrial cristae, abnormal nucleus, loose, rough and thin mesophyll cells, epidermal, cortical, and stellar cells. Deposition of electronically dense materials near cell walls is also observed. These changes in plant cells impact the plant growth. This is the first chapter to highlight the toxicity of nanoparticles on the plants at anatomical and ultrastructural level.

Keywords Anatomy · Chloroplasts · Nanoparticles · Toxicity · Xylem

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13.1 Introduction

The term “nanotechnology” was coined by Norio Taniguchi and introduced to the world by Eric Drexler (Eric 1986; Taniguchi 1996). Nanoparticles are receiving great attention due to their unique properties and wide range of applications as coatings, consumer products, cosmetics, chemicals, electronics and optics, environmental remediation, food, fuel additives, textile industries, medical industries, paints, plastics, wastewater treatment, and as a nano-fertilizer (Rajput et al. 2017a, b, 2018a). Most of the research on nanoparticles is directed to its efficiency in medicine and agriculture sectors and increasing rapidly on new characteristics with huge investments by public and private sectors. The global nanotechnology market in environmental applications reached \$23.4 billion in 2014 and is expected to be \$41.8 billion by 2020 (BBC 2015), whereas, global nanocomposite market, in value term, should reach \$5.3 billion by 2021 from \$1.6 billion in 2016 (McWilliams 2017). The global market for metal-oxide nanoparticles is likely to increase from 0.27 million tons (2012) to 1.663 million tons by 2020.

Data based on modeling analysis indicates that the production, use and disposal of various metal-based nanoparticles leads to release of thousands of tons of most common nanoparticles (Ag, Al, Ce, Cu, Fe, Ti, and Zn) into environment each year with majority of them end up in the soil, directly or through landfills from sludge and other waste. Other components of biosphere, water, and air are also receiving the significantly high number of nanoparticles’ share (Keller et al. 2013). Although, the estimated concentration of nanoparticles in the environment may not be entirely accurate as the values are indicated by predictive calculations (Sun et al. 2014). Sources of nanoparticles entry into the environment are divided as a natural and anthropogenic activity. Many anthropogenic objects and processes are sources of nanoparticles entry into the environment intentionally or accidentally. There are four major sources of nanoparticles emanation into the environment. Namely, manufacturing of raw materials, nano-enabled products, product use, and waste management services (Tolaymat et al. 2017). Being released into the soil and water, nanoparticles can transport from one place to another and settle as soil sediments. Soil contaminated with nanoparticles can pollute the groundwater (Rajput et al. 2018a; Tripathi et al. 2011). Nanoparticles being highly reactive particles can interact with other pollutants and form new compounds. The introduction of nanoparticles in the food chain via growing agricultural plants in contaminated soils might impose a serious threat to the human health (Rico et al. 2011). Up to 99% of TiO_2 nanoparticles remain within the sludge of wastewater treatment plants (Tourinho et al. 2012). Microorganism’s presence in this sludge could transform nanoparticles even more toxic substance, for example, selenate and selenite (Jain et al. 2016). Soil is the environmental matrix, rich in natural nanoparticles both primary and agglomerates/aggregates. Soil and plants are closely linked in “soil-plant system,” where a potential direct impact of nanoparticles in soil may harm microorganisms and plants, consequently, affect consumers such as animals and human beings.

Metal-based nanoparticles (CuO, ZnO, Ag, TiO_2, and Fe_3O_4) are widely being used in agriculture and medical sector. According to recent studies metallic nanoparticles have a dual impact on plants: low concentrations could have a positive impact and high concentrations impose threat to plants growth and developments (Jha and Pudake 2016). Phytotoxicity of nanoparticles is difficult to assess because it depends on several factors, for instance, physical nature, synthesis and production method, coating materials, size and structure of nanoparticles, plant species, mode of applications, and plant growing techniques (hydroponic, pot/model or in soil medium). Therefore, it is reasonable to speculate the consequences of the unregulated use of nanoparticles in agriculture and food industry.

Plants are one of the most important entities and provide very large surface area for nanoparticles exposure via roots and upper ground parts (Dietz and Herth 2011). Terrestrial species can have more interactions with nanoparticles because up to 28% of the total nanoparticles production ends into soils (Keller and Lazareva 2013). As nanoparticles are very small in size and have potential to enter, translocate, and penetrate the physiological barriers to travel within the plant tissues. Therefore, it is necessary to monitor long-term effects of nanoparticles in plant systems, however, few studies are available which indicates that the nanoparticles may cause morphological, physiological, genetic, and epigenetic changes and alter the plant growth and nutritional status (Rajput et al. 2018a). Several researches reported negative, positive or neutral effects of nanoparticles on plants performance. It is well understood that nanoparticles enter plant tissues either via root (root tips, rhizodermis, and lateral root junctions) in case of soil application of nanoparticles or the above-ground tissues (cuticles, trichomes, stomata, stigma, and hydathodes) as well as through the wounds and root junctions in case of foliar applications. The air-dispersed nanoparticles may penetrate and transport via the stomatal openings (Pullagurala et al. 2018; Raliya et al. 2016). Exposure with plant tissue, nanoparticles penetrate into the cell wall and cell membrane of epidermis, cortex of root accompanied by a complex series of events to enter plant vascular bundle (xylem) and move to the stele. Xylem serves as the most important vehicle in the distribution and translocation of nanoparticles to leaves. Epidermis, cortex, endodermis, cambium, and xylem accumulate higher nanoparticles than other plant tissues. The mechanism of nanoparticles uptake is generally considered as an active-transport mechanism that includes several other cellular processes such as signaling, recycling, and the regulation of plasma membrane (Etxeberria et al. 2009). Once nanoparticles penetrate the plant roots, it moves in plant tissues by the apoplast and symplastic ways and translocates via cytoplasm to the photosynthetic system (Pérez-de-Luque 2017). Apoplastic transports take place outside the plasma membrane and allow radial movement within the plant tissues (Sattelmacher 2001), whereas, symplastic transport involves movement of water and substances between the cytoplasm of adjacent cells (Roberts and Oparka 2003). The foliar application on nanoparticles needs to cross the cuticle layer either via lipophilic or the hydrophilic pathway (Pérez-de-Luque 2017). Zinc oxide and other oxide nanoparticles internalization happen in the plant cells via apoplastic pathway. The use of confocal microscopy revealed that the aggregates of ZnO nanoparticles entered the corn root epidermis and cortex via apoplastic pathway and passed the endodermis through the symplastic pathway (Zhao et al. 2012). Magnetic carbon-coated nanoparticles can easily penetrate cultivated crop plant's root by forming a biocompatible magnetic fluid known as bio-ferrofluid (Cifuentes et al. 2010). The significant amount of Fe_3O_4 particles suspended in a liquid medium was taken up and translocated throughout the pumpkin plant's tissues at concentration of 0.5 g L^{-1} (Zhu et al. 2008). However, metal-tolerant plants could limit nanoparticles uptake into the photosynthetic tissue by restricting the transport across the root endodermis and storing them in the root cortex, whereas, hyper-accumulating plants accumulate excess amounts of nanoparticles in the harvestable tissues (Manceau et al. 2008). However, the behavior of various nanoparticles in plants is not entirely clear. According to research reviewed by Rajput et al. (2019), several possible mechanisms exist. Nanoparticles could decompose directly in the soil and produce ions, which may be incorporated in the plant system. Large nanoparticles may first decompose in soil and produce smaller nanoparticles, which may be incorporated in plant tissues. Alternatively, these smaller nanoparticles may further decompose forming ions, which can be incorporated in plant tissues.

The present chapter has been aimed to combine all the previous studies and reveal the toxicity of nanoparticles on anatomical and ultrastructural modifications in plant cells.

13.2 Structural and Ultrastructural Changes

Nanoparticles interact with plant tissues by various routes of application in agriculture, accidental discharges, water remediation, irrigation water, and aerial deposition or presence in the soil. Plants need little amounts of trace elements; therefore, excess concentration in soil may affect plant performance. However, trace elements are important because of their association with environmental issues and the health of plants, animals, and humans, for example, Cu and Fe is an essential component of chlorophyll (Norton et al. 2012). Several studies are conducted to observe nanoparticles toxicity on seed germination, root and shoot growth, morphological and physiological changes in plants (Rajput et al. 2018a). To notice structural and ultrastructural changes induced by nanoparticles is a very difficult task, and even more difficult to find the accumulation of nanoparticles in plant tissues. However, there are several studies indicate the clear damages to plant cell organelles (Rajput et al. 2018a, b, c, d). Most common changes were observed in cell organelles such as plastids, thylakoids, mitochondria, peroxisomes, plastoglobules, starch granules, protoplasm, vascular bundles, plasma membrane, cell wall, root morphology, epidermis, endodermis, vascular bundle, and central cylinder (Table 13.1; Fig. 13.1).

Table 13.1 Structural and ultrastructural modifications in plants induced by nanoparticles

Nanoparticles	Concentrations	Plant species	Toxic effects	References
Ag	10 mg L^{-1}	*Spirodela polyrhiza*	Larger starch granules, fewer intergranal thylakoids in chloroplast	Jiang et al. (2014)
Ag, $AgNO_3$	25, 50, 75, 100, or 500 μM	*Nicotiana tabacum*	Partially destroyed and vacuolated root cells, destroyed nuclei, visualized black dots near and inside the cell wall of root cells, disorganized and smaller sizes of plastid were observed	Cvjetko et al. (2018)
Ag, ZnO, AgNO, $ZnSO_4$	73.4, 1000 μg mL^{-1}	*Zea mays* L., *Brassica oleracea var. capitata* L.	Metaxylem counts increased, $AgNO_3$ leads erosion in maize root apical meristem	Pokhrel and Dubey (2013)
CeO_2	0, 100, 400 mg kg^{-1}	*Triticum aestivum* L.	Changed leaf cells microstructure, swollen chloroplasts, squeezed nuclei, bent and loosely arranged thylakoids, decreased chlorophyll	Du et al. (2015)
Co_3O_4	1.0 mg mL^{-1}	*Solanum melongena* L.	Degeneration of mitochondrial cristae, abundance of peroxisomes and excessive vacuolization were observed	Faisal et al. (2016)
CuO	0, 5, 25, 50 mg L^{-1}	*Quercus robur*	Disturbed the shape of plastoglobules and starch of leaves cells	Olchowik et al. (2017)
CuO	0.1, 1.0, 10.0 g L^{-1}	*Landoltia punctata*	Plastoglobules increased, size of starch grains decreased, mitochondria appeared to be disrupted and irregular in shape, stroma displaced the grana and dilation of the chloroplast membrane	Lalau et al. (2015)
CuO	1000 mg L^{-1}	*Oryza sativa*	Decreased thylakoids number per granum, swelled intrathylakoidal space	Da Costa and Sharma (2016)
CuO, Al_2O_3	20–2000 μg mL^{-1}	*Solanum lycopersicon*	Increased periplasmic spaces of confluent parenchymal cells and dark aggregates, and spots were found in vacuoles	Ahmed et al. (2018)
Fe	0.05, 0.1, 2 mM	*Capsicum annuum*	Altered the leaf organization and increased chloroplast number, grana stacking, thinner mesophyll cells tightly packed looser	Yuan et al. (2018)

(continued)

Table 13.1 (continued)

Nanoparticles	Concentrations	Plant species	Toxic effects	References
NiO	0.025–2.0 mg mL^{-1}	*Lycopersicon esculentum*	Condensed nucleus, abundance peroxisomes, deteriorate mitochondrial cristae in root cells	Faisal et al. (2013)
nZVI (nano zerovalent iron)	0.5 g L^{-1}	*Arabidopsis thaliana*	Reduction in cell wall thickness and disturbed orientation of cellulose microfibrils	Kim et al. (2014)
ZnO	1000 mg L^{-1}	*Lolium perenne*	affected root tip morphology, highly collapsed cortical cells, broken epidermis and root cap, vacuolated cortical cells and shrank vascular cylinder	Lin and Xing (2008)
ZnO, ZnO bulk particles	100 mg L^{-1}	*Brassicanapus* L.	Decreased root tip diameter and size of epidermal and cortical cells, increased stellar cells and decreased size, size of pericycle cells also decreased, affected shape and ultrastructure of chloroplasts of mesophyll cells, decreased size and increased number of plastoglobuli	Kouhi et al. (2015)
CuO	10 g L^{-1}	*Hordeum sativum* distichum	Swollen chloroplasts with their shear area, decreased the number of plastoglobules, increased the areas of plastoglobules, rare starch granules with bigger size	Rajput et al. (2018c)

13.2.1 *Effects of Nanoparticles on Above-Ground Plant Tissues*

Chloroplasts, mitochondria, and peroxisomes are major organelles in the glycolysis cycle of photosynthesis, which is the source of intermediate substances needed for different synthesis to ensure the plant growth (Van Dingenen et al. 2016). Chloroplasts are the most vulnerable organelles in plant. Anatomical modifications in chloroplast would affect the light path and consequently affect the photosynthesis (Zhang et al. 2010). Photosynthesis is a key process for the conversion of light energy into chemical energy, which is performed by chloroplast, and components of the photosynthetic machinery embedded in a highly dynamic matrix such as thylakoid membranes (Rottet et al. 2015). Thylakoids play an important role in the

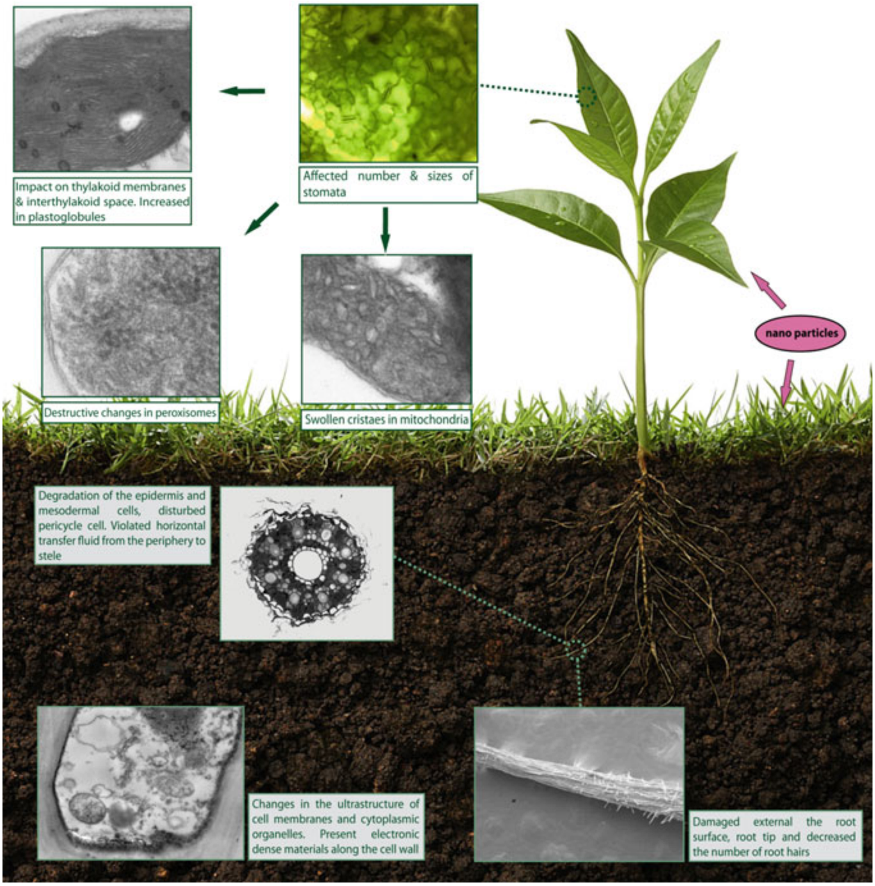

Fig. 13.1 Schematic on effects of nanoparticles on anatomy and ultrastructure of plant tissues

photosynthesis as the light reaction occurs at the thylakoid membrane (Järvi et al. 2013). At the curved regions of the thylakoid membrane, globular lipid droplets are embedded, named plastoglobules a lipoprotein particle surrounded by a lipid monolayer, structurally and functionally associated with the thylakoid membranes via the outer lipid leaflet in chloroplasts (Kessler and Vidi 2007). Plastoglobule can be an oval or tubular shape. Any changes in mitochondrial cristae may trigger the biogenesis of peroxisomes as a consequence of stunted root growth detoxifies the intracellular reactive oxygen species (Faisal et al. 2013). Therefore, it is important to observe the toxicity of nanoparticles on ultrastructure of chloroplast and mitochondria. Austin et al. (2006) demonstrated that plastoglobules attach to thylakoids through a half-lipid bilayer and plays a crucial role in lipid biosynthesis. To relate enzymatic activities of plastoglobules to chloroplast functions, the author investigated spatial relationship between plastoglobules and thylakoid membranes by high-pressure freezing/freeze-substitution techniques and characterized the structures by a combination of electron tomography, immunoelectron tomography, and freeze-fracture (-etch) methods. These techniques revealed that plastoglobules constitute a distinct structural and functional subcompartment of thylakoids, which contain both lipid-binding protein and enzyme involve in lipid biosynthesis and metabolism.

A relatively poor known data demonstrating the influence of nanoparticles on the photosynthesis are mainly descriptive and are based on routine procedures of photosynthesis researches; pulse-amplitude modulation (PAM), chlorophyll fluorometer and gas-exchange studies (Da Costa and Sharma 2016; Li et al. 2018). In these studies, nanoparticles are usually considered to be involved in micronutrition and, more often in ecotoxic studies. Metal-oxide nanoparticles were attempted to apply as micronutrients. Thus, Fathi et al. (2017) have shown that ZnO and Fe_2O_3 nanoparticles (foliar spray) decreased negative consequences of salt stress indicated by root growth rate and net CO_2 assimilation rate. At that time, maximal quantum yield of photosystem II (Fv/Fm) was slightly decreased with this treatment, which does not seem surprising in regard to the known data on increasing the proportion of cyclic electron transport around PSI in total photosynthesis under salt stress. In contrary, ZnO nanoparticles were shown as a phytotoxic compound (Tripathi et al. 2017). ZnO nanoparticle reduced Fv/Fm and photochemical quenching of fluorescence (qP) due to increased accumulation of zinc in xylem and phloem. This negative influence can be decreased with sodium nitroprusside as a donor of nitric oxide. Toxic effect of CuO nanoparticles was shown in experiments with *Oryza sativa*. CuO nanoparticles decreased Fv/Fm up to a complete loss of PSII photochemical quenching at concentration of 1000 mg L^{-1} and declined the photosynthetic pigment contents (Da Costa and Sharma 2016). CuO nanoparticles toxicity was also studied in experiments using chlorophyll fluorescence imaging method where it was shown that CuO nanoparticles inhibited PSII maximal (Fv/Fm), PSII operational quantum yields, and qP associated with electron transport.

Various Cr_2O_3 nanoparticle suspensions (0.01, 0.05, 0.1, and 0.5 g L^{-1}) significantly inhibited the growth of soybean, and besides, Fv/Fm and qP that was caused by the destruction of chloroplast thylakoids structure (Li et al. 2018). Shaw et al. (2014) reported CuO nanoparticles reduced photosynthetic performance index of *Hordeum vulgare* and Ahmed et al. (2018) indicated CuO and Al_2O_3 affected the photosynthesis of tomato leaf by decreasing the surface area and photosynthetic pigment. The recent study on CuO nanoparticles toxicity on spring barley showed swollen chloroplasts increase the size of plastoglobules, starch grains, and decreased counts of plastoglobule (Rajput et al. 2018c). It might be a protective mechanism against damage to the photosynthetic apparatus (Rajput et al. 2018a). It is also reported that the mung-bean and wheat plant uptake, bio-accumulate, and translocate CuO nanoparticles within the tissues (Lee et al. 2008). Nhan et al. (2015) found swollen and ruptured external surface of chloroplast in Bt-transgenic cotton leaves polluted by CeO_2 nanoparticles. Cvjetko et al. (2018) observed the changes in the size of chloroplast in Ag nanoparticles-treated and $AgNO_3$-treated tobacco leaves. Ag nanoparticles affected chloroplast ultrastructure by disorganizing the chloroplast, grana, and thylakoids of barley leave grown in a model experiment (Fayez et al. 2017). There is evidence of foliar uptake of nanoparticles (Fe_2O_3, TiO_2, MgO, and ZnO) and their translocation to roots through sieve elements (Chichiriccò and Poma 2015). Olchowik et al. (2017) explore the effect of Ag and Cu nanoparticles on the seedlings of *Quercus ribur* L. by foliar application at four concentrations 0, 5, 25 and 50 mg L^{-1}, and observed ultrastructure disturbances such as abnormal shape of chloroplasts and disturbances in plastoglobules as well as in starch content treated with 50 mg L^{-1} Cu- and Ag nanoparticles. Ag nanoparticles decreased the size and numbers of plastoglobules compared with untreated plants. By contrast, Ag nanoparticles-treated plants contained the bigger size of starch grains in plastids. Variously, Ag nanoparticles impaired structure of thylakoid membrane in *Arabidopsis thaliana* (Qian et al. 2013). Arsenic affects plant growth and disturbed the cell ultrastructure in rice throughout the modulating of proteins involved in metabolism and redox homeostasis. Although there were no visible symptoms on leaves, the treatment of 100 and 200 μM arsenic resulted in the swollen grana (Liu et al. 2013). Giraldo et al. (2014) showed that single-walled carbon nanotubes (SWNTs) and cerium carbon-based NPs localize the envelope of chloroplast extracted from spinach leaves enhance three-times ROS scavenging. It seems that the woody plants respond under nanoparticles toxicity alike the crop plants.

Phytotoxicity and negative influence on photosynthesis of metal-oxide nanoparticles were also shown for aquatic plants. The sources of nanoparticles occurrence in aquatic ecosystem could be several. Naturally generated nanoparticles as xenobiotic substances could have a great impact on aquatic biota as well as constitute danger for terrestrial environment (Moore 2006). Silver nanoparticles and $AgNO_3$ significantly decreased the biomass of *Spirodela polyrhiza*, as well as chlorophyll a (Chl a) content, chlorophyll a/b ratio, and Fv/Fm (Jiang et al. 2012). The similar results were obtained in the study on the influence of silver nanoparticles on marine diatom *Skeletonema costatum* (Huang et al. 2016). A study showed that CuO nanoparticles alone (0.004 g L^{-1}) is less toxic than CuO nanoparticles coated with polymer to green alga (*Chlamydomonas reinhardtii*) after 6 h of exposition (Melegari et al. 2013). Nonetheless, it still decreased activity of PS II and was found responsible for generation of reactive oxygen species (ROS). The production of ROS may be the result of conditions when plants are subjected to harmful stress conditions. The chloroplasts and mitochondria of plant cells are important in intracellular generators of ROS. Internal O_2 concentration is high during photosynthesis, and chloroplasts are particularly prone to generate ROS; therefore, these cytotoxic ROS can remarkably disrupt normal metabolism through oxidative damage of lipids, nucleic acids, and proteins (Melegari et al. 2013; Perreault et al. 2014; Song et al. 2016). In general, it may be possible to agree with the conclusion that the declining photosynthetic efficiency is a good predictor of nanoparticles toxic effects on aquatic plants (at least on phytoplankton) revealed at a population level (Miller et al. 2017). Beside the photosynthesis apparatus and chloroplasts ultrastructure, several other cellular and subcellular organs were found affected by CuO nanoparticles, for example, deformed and shrunken leaf cells, enlightened mitochondria matrix and swollen cristae, and decreased number and size of stomata in spring barley leaves (Rajput et al. 2018b).

13.2.2 Effects of Nanoparticles on Plant Root Tissues

Structural changes in epidermis and endodermis impede the radial transport of fluid to the root from the peripheral areas and may be one of the causes for a decline in both sequestration and translocation of mineral nutrients from the roots to above-ground tissues of plants. It was observed excess Cu accumulates in vacuoles and cell walls (MacFarlane and Burchett 2000; Vesk et al. 1999). Asztemborska et al. (2015) found the highest content of Al accumulated in roots of *Allium cepa*, *Lepidium sativum*, *Zea mays*, and *Kalanchoe daigremontiana* treated with Al_2O_3 nanoparticles. Cvjetko et al. (2018) revealed that the 100 μM concentration of both Ag nanoparticles and $AgNO_3$ induced the high vacuolization of root cells compared with control and root cells partially destroyed. Faisal et al. (2013) suggested that NiO nanoparticles successfully pierced the tomato roots and formed agglomerates. NiO nanoparticles increased antioxidant activities and ROS generation, increased the number of apoptotic and necrotic cells, and ultrastructural analysis showed nuclear condensation, abundance in peroxisomes and degenerated mitochondrial cristae.

It is reported that the nanoparticles more aggregate in soil due to organic matter, which reduces their transport to plants (Ahmed et al. 2018). Cross semi-thin sections of root cells treated by ZnO nanoparticles and ZnO bulk particles analyzed by light microscope showed that root tip diameter was decreased in both treated plants compared to the control, bulk particles decreased the size of the epidermal and cortical cells, and both particles affected stellar and pericycle cells (Kouhi et al. 2015). Disturbances in the cell wall integrity of epidermis and endoderm, vacuolization and disorganization of endoplasmic reticulum fragments, swelling of mitochondria, and destruction of mitochondrial cristae were noted in roots of *Hordeum sativum* distichum treated with high concentration of CuO nanoparticles (Rajput et al. 2018b). Similarly, other nanoparticles also affected plant root cells, for instance, Ag nanoparticles induced the high vacuolization, and partially destroyed nuclei of *Nicotiana tabacum* (Cvjetko et al. 2018), abundance peroxisomes and deteriorated mitochondrial cristae in *L. esculentum* treated by NiO nanoparticles (Faisal et al. 2013), ZnO nanoparticles collapsed cortical cells, broken epidermis, vacuolated cortical cells, and shrank vascular cylinder in *Lolium perenne* (Lin and Xing 2008), increased metaxylem counts in *Zea mays* treated by Ag nanoparticles (Pokhrel and Dubey 2013), highly vacuolated cortical, disrupted epidermal root cells of *Lolium multiflorum* treated by Ag nanoparticles (Yin et al. 2011). Destructive changes in structure and ultrastructure of these organelles are associated with altered plant growth and performance. Nanoparticle used in the forest or agro-production is not only influenced host plants but also affect root-associated organisms. Mycorrhizal symbiosis is a type of mutualistic association with woody plants and these associations are essential as they are known to enhance the growth of plants by nutrient transfer especially phosphorus (P). Deployment of nanoparticles (as growth stimulators or plant protection agents) in the agricultural production is linked with certain dangers that influences on both host plant and mycorrhizal partner will prove unfavorable. While, some studies suggest that at low concentration, there is no discernible impact on levels of mycorrhizal colonization, even if high concentrations do indeed seem to curb this (Cao et al. 2017; Judy et al. 2015), others point to a negative influence of nanoparticles on the mycorrhizal colonization of plant roots (Dubchak et al. 2010). Feng et al. (2013) reported a stimulatory influence of AgNPs on the formation of arbuscular mycorrhizae in any of concentrations investigated. The formation of mycorrhizae was observed in research, in which Ag nanoparticles were applied as an alternative to fungicides (Olchowik et al. 2017). In another study, Sweet and Singleton (2015) shown reduce not only the level of mycorrhization but also the biodiversity of ectomycorrhizal fungi (EMF) after application of Ag nanoparticles in pine seedlings. At high concentration Ag nanoparticles, no EMF were observed. Metallic nanoparticles mobility and uptake in plants depend on symbiotic microenvironments. Feng et al. (2013) shown that mycorrhizal fungi increased the soil porosity near nano-Ag and nano-FeO exposed roots of *Trifolium repens*. Fungi symbionts play a major role in soil mineral weathering and also protect roots from abiotic stress such as heavy metals (Smith and Read 2008). It is also reported that arbuscular mycorrhizal fungi could help to transform copper into metallic Cu nanoparticles found near plants root (Manceau et al. 2008).

13.3 Conclusion and Future Prospective

Present chapter could help to increase the scientific understanding of nanoparticles toxicity on plant tissues. Electronic and light micrograph of several studies on nanoparticles toxicity on various plant species indicates damages to plant tissues and deposition of electronically dense materials near cell wall and disturbed vascular bundles. The studies on nanoparticles toxicity on plant also indicate the decreases in germination rate, chlorophyll fluorescence, transpiration, the root and shoot length, and affected stomatal aperture. Most of the studies are addressing the impact of single nanoparticles on plants. Due to a widespread use of nanoparticles in industrial and domestic scale makes co-occurrence of different nanoparticles inevitable.

Available data and studies on nanoparticles remain unresolved a few basic questions related to the mechanisms on how nanoparticles affect fluid translocation and photosynthesis. They are: (a) do the nanoparticles directly penetrate to root and chloroplasts or thylakoids?; (b) are the nanoparticle involved in the process of cell autophagy?; (c) what chemical transformations of nanoparticles occur (or do not occur) in plants, and how their by-products (if exist) can affect plant growth?; (d) what is the molecular target of nanoparticle within the electron transport chain, Calvin cycle and other photosynthetic compartments? Evidently, these and other questions may be a central aim of the future research. The critical assessment of mechanistic aspects of nanoparticles behavior in the sustainable environment should be monitored.

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Part II

Nanomaterials in Horticulture and Forestry

Chapter 14
Nano-Enabled Technological Interventions for Sustainable Production, Protection, and Storage of Fruit Crops

Gurteg Singh and Anu Kalia

Abstract Agri-nanotechnology, an active and emerging field of research and development (R&D), hails research on improved and balanced nutrition through the use of nano-fertilizers, and targeted and sustained release of active ingredient from nano-pesticides. Furthermore, nano-interventions include proper monitoring of a variety of factors such as soil edaphic, abiotic (temperature, moisture, pH, nutrient content), and biotic (pest and pathogens) by employing *in planta*/in situ/ex situ portable sensor systems for fruit crops. Numerous post-harvest management applications have also been reported, including the development of efficient nano-enabled packaging and processing systems. However, this upcoming technology is yet in its developmental stages and is likely to be commercialized. Nonetheless, the anticipated benefits will fuel further progress in this field in the coming years. The chapter reviews all these aspects in relation to fruit crops.

Keywords Nanoscale · Agri-innovations · Sustainability · Shelf-life enhancement · Targeted release · Nutrient use efficiency

14.1 Introduction

Technology intrusion in agri-sector is noteworthy, particularly in the Green Revolution (GR) era. However, the post-GR complications led to a novel renaissance of the concept of ‘Evergreen Revolution’ which can be demarcated by the

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production of sufficient, healthy, and safe food for the growing population in a sustainable manner. Sustainable agricultural production systems are the most desirable. However, to achieve quantum production of sufficient quantity and quality of products without degradation of the environment, particular mention for maintenance of soil health under changing global climate conditions is the biggest challenge for the present-day agri-researchers. Moreover, to meet the nutritional security of the growing population and alteration in the food habits and predominance of fruits among the urban diet culture has escalated the demand for fruit crops (Foley 2011). To meet the global demand for horticultural produce, there is a need to increase production efficiency and to decrease the post-harvest losses by use of novel scientific technologies such as biotechnology and nanotechnology. It has been estimated that around 20–30% of the horticultural product is wasted in developing countries, so even 5–7% reduction in post-harvest losses may contribute a huge save. This will not only improve the farmer's income but also will encourage more consumption of highly nutritious fruit in the developing countries.

14.2 'Nano': The Sphinx Technology

Nanotechnology (NT), the sixth revolutionary technology after the Green Revolution and biotechnology revolution in the 1960s and 1990s, has emerged as a multidisciplinary field aiming novelty, high-growth, and pertinent broad impacts (Mishra et al. 2016). It involves a study of nanoscale (1–100 nm) materials known as nanoparticles (NPs) (Olsman and Goentoro 2018), exhibiting unique and novel physical, chemical, and biological properties (Li et al. 2001). Agri-nanotechnology (Agri-NT), application of NT know-how, its products and devices to modernize agriculture and farming, has been the recent prima foci of researchers across the globe (Nair et al. 2010). Therefore, NT offers renaissance of plant nutrient products, plant growth-enhancing substances, as well as pest and disease diagnostics techniques (Duhan et al. 2017). It has led to the development of innovative tools that have revolutionized the agricultural and food industry. Further, it has already brought tremendous benefits to farmers, the food industry, and consumers alike, through improved innovation in pre- and post-harvest management of agri-food (FAO/WHO 2010). This creates an excellent opportunity to address complex technical issues related to supply chain processes associated with food quality, handling, packaging, and safety.

14.3 Nano-Revolution in Horticulture

The application of products of nanotechnology for proper post-harvest management and enhancement of the shelf life of the produce (particularly the fruits and vegetables) has already been a commercial success (Kalia and Parshad 2015;

Table 14.1 Biological synthesis of nanoparticles and their possible applications for decreasing the post-harvest losses and enhancement of shelf life of horticultural crops

Biological source	NP generated	Unique property	References
Bacillus circulans	ZnO	Antimicrobial potential toward *E. coli, E. cloacae* and *S. aureus*	Kaur and Kalia (2016)
Pleurotus florida			
Bacillus circulans	ZnO	Enhanced shelf life of Peach fruit	Kaur et al. (2016b)
Pleurotus florida			
Trichoderma harzianum	Ag NPs	Anti-mycotic activity against *Fusarium moniliforme*	Kaur et al. (2016a)
Urtica diocia leaf extracts	ZnO, CuO	Enhanced shelf life of guava	Kaur et al. (2016c)
Trichoderma harzianum	Ag NPs	Phyto-promotional and flower induction properties in potato	Sharma et al. (2016)

Hamad et al. 2018; Kim et al. 2018). However, research interventions are incipient though paving towards materialization of the concepts of enhanced input use efficiency and higher productivity through use of nanomaterials or the nano-enabled or derived devices for obtaining higher yields with lower/judicious use of agri-inputs in horticultural crops (Martinelli et al. 2016; Pestovsky and Martínez-Antonio 2017) (Table 14.1).

Horticultural crops are more or less perishable and the degree of standardization of some kinds of fruit products, and their management is still low. The studies confirm that nanotechnology can be used for controlling growth and contamination by microorganisms, development of new generation of packaging systems with increased strength, quality, and appearance, reduction the effects of gases and the harmful rays (UV), and use of the multiple nano-biosensors to monitor the quality (Yadollahi et al. 2010; Mousavi and Rezai 2011; Ditta 2012). With these applications, the issues related to the biosafety of this technology and to improve the awareness about this technology are emerging (Mishra et al. 2016). The studies on interactions between nanoparticles and plant responses can bring revolution in crop production through efficient nutrient use and increased disease resistance, and yield (Wang et al. 2016). However, the economic benefits of this technology in horticultural crops are no more different from the application of other new technologies.

14.3.1 Nano-Nutrients for Enhanced Fertilizer Use—Efficiency in Fruit Crops

Irrigation and fertilizer application are two important practices which affect the extent and quality of plant growth and hence plant productivity. It has been reported that only 30–60 percent of nitrogen, 10–20 percent of phosphorus, and 30–50 percent of potassium of the applied fertilizers are absorbed by the intended plants and rest are lost to the environment (Corradini et al. 2010). In addition to the monetary and resource losses, it results in environmental pollution. For increasing the productivity, efficient utilization of fertilizers is highly required.

Fruit crop productivity is lowered under nutrient-deficient conditions and thus optimization of fruit yield and quality requires pertinent nutrient management of the orchards (Carranca et al. 2018). Yield maximization in nutrient-poor, problematic, and/or unproductive soils with the application of nutrient use efficient formulations of fertilizers is one among the daunting challenges of precision agricultural practices (Srivastava 2015; Khan et al. 2017). As fertilizer application is prerequisite for ensuring high plant-available forms of nutrients in soil, yield enhancement through the use of novel formulations of the slow, controlled, and targeted release fertilizers is desirable.

Nano-fertilizers are emerging as prospective agri-inputs to improve growth, yield, and quality parameters of the horticultural produce (Davarpanah et al. 2016; Kim et al. 2018). These fertilizers exhibit better nutrient use efficiency, thereby reducing the wastage of the applied fertilizer and incentivize environment protection by minimization of cultivation costs and the efforts required for reclamation of the polluted niches (Liu and Lal 2015, 2016; Singh et al. 2017; Qureshi et al. 2018). Moreover, these products aim at controlled and targeted delivery of the nutrient(s) temporally or spatially in accordance with the critical crop growth stage or the root zone and may provide nutrient throughout the crop growth period eventuating the concept of precision agriculture (Bindraban et al. 2015; Dimkpa and Bindraban 2017; Duhan et al. 2017; Pestovsky and Martínez-Antonio 2017).

Nano-fertilizers can be categorized as nanoscale elements having direct nutritional relevance and non-nutrient nano-elements of indirect role for growth and yield enhancement (Liu and Lal 2016). Fruit crops require macro- as well as micronutrients including NPK, Mg, and Ca among the former and B, Fe, Zn, and Mn representing the latter group (Tanou et al. 2017). These fertilizers are primarily applied to plants by soil, i.e., broadcasting, trench and/or pit application as basal dose, through fertigation and foliar sprays as growth-stimulating and preventive or nutritional deficiency correction dose (Fernández and Brown 2013). Foliar applications have certainly been advantageous to obviate the soil application drawbacks of conventional fertilizers (Ali et al. 2014). Primarily, the conventional fertilizers exhibit low use efficiency due to fixation and precipitation in soil and thus remain in plant-available forms for a short span (Alshaal and El-Ramady 2017). Therefore, higher amounts and concentrations of bulk fertilizers are applied considering the losses incurred due to complexation with other salts in soil matrix followed by fixation and precipitation of the applied fertilizers. Therefore, foliar sprays for supplying additional N, P, K, sulfur (S), magnesium (Mg), and micronutrients are generally recommended (Alshaal and El-Ramady 2017). These preventive foliar sprays of macro- and micronutrients can help to decrease the incidences of nutrient deficiency disorders in fruit crops. The benefits of the foliar fertilizer application are manyfold as it ensures customized delivery of nutrients as per internal demand of plant at critical vegetative and reproductive stages (Fernández and Brown 2013) and also leads to enhancement in fruit yield compared to soil application as nutrient supply becomes a ‘limiting’ factor

(Kannan 2010). However, there are few critical factors that may affect the success of foliar-applied nutrient fertilizers such as leaf age (young, immature to mature leaves) and pH of the spray liquid which are important for foliar absorption, while the occurrence, amount, chemistry of the lipophilic cutin and cuticular wax and cuticular sculpturing, surface heterogeneity due to the presence of trichomes and epicuticular pores and occurrence of different nano- to microscale epidermal cell gradients may also affect the absorption of the foliar-applied fertilizers (Fernández and Brown 2013; Alshaal and El-Ramady 2017).

Similar to conventional fertilizers, the nanoscale macro- and micronutrient fertilizers have preferably been applied as foliar sprays (Bala et al. 2019), though the fertigation through drip irrigation systems, soil applications, seed or seedling dipping treatments and seed priming have been evaluated on several crops (Li et al. 2016). Crops of horticultural importance, particularly fruit trees, exhibit substantially reduced fruit yield besides decrease in the quality parameters, shorter shelf life, and inferior merchandisable value under micronutrient deficiency conditions (Li et al. 2016; Tanou et al. 2017). Thus, foliar application of nanoscale nutrient fertilizers particularly the micronutrients can enhance the fruit yield and productivity (Table 14.2). Interestingly, the non-nutrient engineered nanomaterials (ENMs) including metal/nonmetal oxides, and noble metal NPs can also be considered nano-fertilizers provided their application alters the host-plant metabolism, thereby increasing photosynthetic rate, biomass accumulation, and finally the yield (Table 14.2).

14.3.2 Nano-Pesticides: Smart Plant Protection Formulations

The pests and pathogens severely affect the yield and crop productivity. Pesticides are formulations containing natural or synthetic organic compounds as active ingredient (a.i.) which on application provide protection from a variety of pest and pathogens. The incidences of development of resistant pest/pathogen(s) and the harmful effects of pesticide usage on nontarget organisms are the critical factors which are driving both research and commercial interests toward the development of new formulations for plant protection (Kalia and Gosal 2011).

Nano-pesticides can be defined as any pesticide formulation that includes entities in the nanometer size range (up to 1000 nm), or active ingredients loaded on nanoscale delivery vehicles (e.g., nanohybrid, nanocomposite) claimed to possess novel properties associated with the small size (Kah et al. 2013; Kah 2015). Conventional pesticides can be categorized on basis of the toxicity and release of the key ingredient such as inorganic minerals, i.e., lead/arsenate and botanicals (first generation), synthetic organic compounds like DDT (second generation), and insect pheromones and growth regulators (third generation) (Hummel 1983; Ramadass and Thiagarajan 2017). However, the nano-pesticides can be classified as

Table 14.2 Effect of nanoscale nutrient fertilizers on growth and yield of fruit crops

Nano-fertilizer evaluated	Size dimensions/other characteristics	Test concentrations	Mode of application	Test fruit crop	Traits evaluated or affected			References
					Vegetative	Yield attributing and yield	Quality attributing	
Micronutrient fertilizers								
Nano-Zn fertilizer	–	0.5 and 1 g L^{-1}	Foliar spray before flowering	Mango (*Mangifera indica* L.) Zebda and Ewasy cultivars	Leaf length Leaf width Total chlorophyll content ↑	Significant increase in panicle length at 7, 21 and 28 days in Ewasy cultivar Significantly higher fruit retention at 48 days Highest fruit weight and yield per tree for 0.5 g L^{-1} Zn spray	TSS: significantly higher in 0.5 g L^{-1} Zn in cv Ewasy Vitamin C: highest amount in cv Zebda @ 1 0.5 g L^{-1}	Zagzog and Gad (2017)
Nano-Zn and boron chelate fertilizer	50 nm (range from 23 to 80 nm)	Zn @ 0, 60 and 120 mg L^{-1} and B @ 0, 3.25 and 6.5 mg L^{-1}	Foliar sprays one week before the first full bloom	Pomegranate (*Punica granatum* cv. Ardestani)	–	Fruit yield ↑ (due to enhanced fruit number per tree)	TSS: 4.4–7.6% ↑ Total acidity:9.5–29.1% ↓ Maturity index: 20.6–46.1% ↑ Juice pH: 0.28–0.62 ↑	Davarpanah et al. (2016)

(continued)

Table 14.2 (continued)

Nano-fertilizer evaluated	Size dimensions/other characteristics	Test concentrations	Mode of application	Test fruit crop	Traits evaluated or affected			References
					Vegetative	Yield attributing and yield	Quality attributing	
Nano-Fe and nano-Zn fertilizer	–	ZnO and FeO NPs @ 150 ppm each	–	Strawberry (*Fragaria* x *ananassa* Duch cv. Chandler)	Plant height ↑ Leaf number Petiole length	Days to 50% flowering ↓ Days to 1st harvesting ↓ Number of fruits plant^{-1} ↑ Fruit weight Fruit diameter ↑ Fruit yield plant-1 Benefit ratio	–	Kumar et al. (2017)
Nano-Fe fertilizer	γ-Fe_2O_3 NPs spherical, average size diameter (20.2 ± 2.7 nm), zeta potential (−11.7 ± 0.1 mV), hydrodynamic diameter (164.5 ± 11.3 nm)	0, 20, 50 and 100 mg L^{-1} as deionized water suspension	Foliar spray every 5 days when the plants had two true leaves	*Citrus maxima* seedlings	Fresh biomass (at higher concentrations) ↓ Leaf wax content↑ Soluble protein content equivalent to control Lipid peroxidation/ MDA: no change Fe content shoot: equaivalent to Fe^{2+} or Fe-Chelate	–	–	Hu et al. (2017)

(continued)

Table 14.2 (continued)

Nano-fertilizer evaluated	Size dimensions/other characteristics	Test concentrations	Mode of application	Test fruit crop	Traits evaluated or affected			References
					Vegetative	Yield attributing and yield	Quality attributing	
Macronutrient fertilizers								
Nano-nitrogen fertilizer	50 nm (range from 23 to 80 nm)	Nano-chelated fertilizer N @ 0.25 (nN1) and 0.5 g N L^{-1} (nN2)	Two foliar sprays at full bloom and a month later	Pomegranate (*Punica granatum* cv. Ardestani)	Leaf N contents increased	Fruit yield: highest 17.8 and 21.9 kg $tree^{-1}$ Fruit number $tree^{-1}$: highest 62.8 and 70.1 $tree^{-1}$ in nN2 (1.8 kgN/ha) treatment	TSS ↑ Aril juice Titrable acidity Total sugars Total anthocyanins ↓	Davarpanah et al. (2017)
Nano-Calcium fertilizer	7–11 nm quasi-spherical calcium nanoparticles	Nano-calcium-yeast nanocomposite at 1, 2 and 3%	Three foliar sprays at full bloom, two weeks after fruit set and one month after the second application	Mango (*Mangifera indica* L. cv. Ewais	Fruit set ↑ Fruit drop ↓ Fruit retention ↑	Fruit weight ↑ Fruit length Fruit width ↑ Peel weight Pulp weight Pulp/seed ratio	TSS ↑	El-Razek et al. (2017)
	Calcium carbonate ($CaCO_3$) NP suspension Average size diameter (60 nm, range 20–100 nm)	26% (v/v) (for field test) vs. colloidal Ca (95% WP)	Two foliar sprays at one-month interval	Tankan (*Citrus tankan*)	Leaf macronutrient contents altered Ca, and N ↑ K content ↓	–	–	Hua et al. (2015)

(continued)

Table 14.2 (continued)

Nano-fertilizer evaluated	Size dimensions/other characteristics	Test concentrations	Mode of application	Test fruit crop	Traits evaluated or affected			References
					Vegetative	Yield attributing and yield	Quality attributing	
	–	Pulverized nano-calcite (0.5 g L^{-1}) + *Ascophyllum nodosum* extract	Four foliar sprays @ 100 L solution per decare at early vegetative followed by 15 days interval	Grapevine (*Vitis vinifera* L. cv. Narince)	Chlorophyll content ↑ Leaf fresh weight ↑	Cluster weight ↑ Pruning weight ↑ Berry weight ↑ Berry volume ↑ Berry length ↑	SSC (○Brix) ↑	Sabir et al. (2014)
Nano NPK fertilizer	–	N (500 and 1000 g $palm^{-1}$ $year^{-1}$) P and K (250 and 500 g $palm^{-1}$ $year^{-1}$)	Directly irrigated with three equal doses at growth start, just after fruit setting and at one month later	Zaghloul date palms	Significantly enhanced leaf area, Chlorophyll contents, total carotenoids, and leaf N, P, and K	Significantly improved yield and bunch weight	Fruit weight ↑ Pulp % TSS Total sugars % Total acidity Fibers % Total soluble ↓ tannins % Nitrate and nitrite	Kh and Refaai (2016)

first-generation nano-pesticides if the nanomaterial exhibits the direct pesticidal action (nano-silver algicides, Nowack et al. 2011) and second generation if the a.i. has been adsorbed, embedded, or encapsulated on or in a nanoscale vehicle (Kah and Hofmann 2014) (Fig. 14.1). The second-generation nano-pesticides predominantly involve reformulations of the a.i. from already existing inventory of the pesticides, though novel nano-formulations may include the encapsulated genes (antisense or RNAi systems) or insect hormones (Kah et al. 2013; Kah and Hofmann 2014).

Another pesticide categorization on the basis of the site of application, uptake, and translocation in the plant has been designated as systemic pesticides, mostly soil/seed applied formulations (as granules or powders or liquid) that are taken up and translocated up through xylem or down through phloem tissue of the plant while non-systemic/contact/trans-laminar pesticides are predominantly applied on foliage or surfaces to curb flying, chewing or sucking pests, and fungal phytopathogens (Vryzas 2016). The environmental toxicity risks are considerable for contact pesticides besides these are hefty for the systemic pesticides, and thus, there is an ardent need for the development of novel nano-enabled formulations of these pesticides which may either involve greater efficacy at low concentrations or possess high degradation potentials in nontarget niches/locations (Kah et al. 2016, 2018; Ramadass and Thiagarajan 2017).

The nanoscale size dimensions of nano-pesticides may impart certain special characteristics to the final formulated product such as greater solubility of poorly water-soluble organic compounds, stability, permeability, and bioavailability (surfactant amended products to alter surface tension properties) of the a.i., slow/ controlled release particularly for encapsulated nano-pesticides, targeted delivery

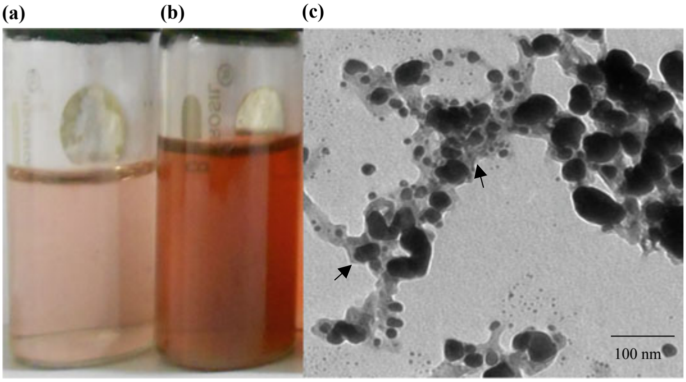

Fig. 14.1 Nanofungicide formulation of biogenic silver nanoparticles showing adsorption of anti-mycotic extracellular proteins derived from biocontrol fungus, *Trichoderma harzianum.* **a** Aqueous nano-dispersion of silver nanoparticles, **b** stable nano-dispersion of silver nanoparticles adsorbing *T. harzianum* proteins, and **c** transmission electron micrograph of bionanocomposite of silver nanoparticles + *T. harzianum* proteins. Solid arrows indicate the silver nanoparticles adsorbing the extracellular macromolecules of biocontrol fungus *T. harzianum*

Table 14.3 Nanomaterials having their role as direct pesticidal action and as pesticide a.i. delivery vector for improved protection from pest and pathogens of fruit crops

Nano-pesticide evaluated	Type and characteristic	Test concentrations/a.i.	Mode of application	Test fruit crop	Lab/pot/field	Target pest/pathogen	Mode of action	References
Nanoparticles having direct pesticidal action								
Calcium carbonate ($CaCO_3$)	NP suspension, Average size diameter (60 nm, range 20–100 nm)	26% (v/v) (for field test) vs. colloidal Ca (95% WP)	Two time foliar spray (@ 3 L per tree) at one week interval	Tankan (*Citrus tankan*)	Field tests	California red scale (*Aonidiella aurantii*) and Oriental fruit flies (*Bactrocera dorsalis*)	Insecticide • Density of red scales and fruit damage by Oriental fruit flies decreased	Hua et al. (2015)
Aluminosilicate (Kaolin or Super Nano and bentonite)	–	1–5% (w/v) of 95% kaolin and 100% bentonite @ 12–16 L tree^{-1}	Foliar spray for twelve Times after every Two weeks	Olive (*Olea europaea*)	Field study	Olive fruit fly (*Bactrocera oleae* Gmelin)	Insecticide • Reduced fly infestation (up to 87%)	Ali (2016)
Zinc/Copper oxide	Size of water dispersed Nordox 30/30 (150–500 nm), Kocide® 3000 (~2–3 µm), ZnO 800 (300–900 nm) and ZnO 400 (200–600 nm)	Range of concentrations (31–500 µg/mL)	Chemicals were incorporated in broth (nutrient broth and brain heart infusion broth/agar)	–	In vitro antimicrobial study using broth microdilution assay	• Gram-negative *Xanthomonas alfalfae* subsp *citrumelonis* (ATCC 49120) *Pseudomonas syringae* pv. *syringae* • Gram-positive *Clavibacter michiganensis* subsp. *michiganensis*	Bactericide MIC values Nordox 30/30 (125–250 µg/mL) Kocide® 3000 (250–500 µg/mL) ZnO 400 and 800 (62.5–125 µg/mL)	Rajasekaran et al. (2016)
Zinc oxide	Zinkicide SG4 (2-D plate-like structure 0.2–0.5 mm range, thickness of ~10.0 nm) Zinkicide SG6 (gel-like structure with interconnecting particles in the 4 to 6 nm range)	10 ml per seedling	Spray on entire plant using an airbrush	Pineapple' sweet orange (*C. sinensis*)	Field study	Citrus canker pathogen (*Xanthomonas citri* subsp. *Citri* strain X2004-0056) inoculated at 10^4 CFU/ml	Bactericide Fruit canker incidence reduced from 63 to 7%	Graham et al. (2016)
Zinc oxide/ Copper oxide	ZnO core material having rod-like (600–1100 nm) structures while ZnO-nCuSi having irregular morphology with 3 to 6 nm Cu-cyrstallites embedded in Si matrix	ZnO-nCuSi (0.22 kg/ha metallic Cu) mixed in water	Foliar spray at 3.0 L per tree with a handgun sprayer at ~21 days interval	*Citrus paradisi* ('Ruby' grapefruit)	In vitro and Field studies	Citrus canker pathogen (*Xanthomonas citri* subsp. *citri*)	Bactericide • Fruit infection incidence reduced to 25% from 60%	Young et al. (2017)

(continued)

Table 14.3 (continued)

Nano-pesticide evaluated	Type and characteristic	Test concentrations/a.i.	Mode of application	Test fruit crop	Lab/pot/field	Target pest/pathogen	Mode of action	References
Sulphr	~35, 55, 87 and 200 nm	For particle size effect, constant 4 mM (0.128 mg mL^{-1}) particle concentration used	0.0128 to 0.0512 mg (from 0.1 to 0.4 mL suspensions) supplemented in PDA	Apple (*Malus pumila* L.)	In vitro spread plate assay on Potato dextrose agar media (poison food technique)	Apple scab pathogen (*Venturia inaequalis* MTCC 1109)	Fungicide • ~35 nm SNPs @ 0.57 mg inhibited ~93% of the fungal growth • Complete inhibition at 0.72 mg conc.	Rao and Paria (2013)
Nano-structures as pesticide delivery vehicles								
Insect pheromone nano-gels	Methyl eugenol encapsulated in 3-D nano-sized fibrillar networks of fiber of diameters ranging from 100–200 nm of low-molecular-mass Gelators (LMMGs) [all-trans tri (p-phenylenevinylene) bis-aldoxime]	12 mg mL^{-1} having 1 ml Methyl eugenol encapsulated in 2.5 mg polymer	Thin polymeric gel films	Guava (*Psidium guajava* Linn.)	Field study	Fruitfly (*Bactrocera dorsalis* Hendel)	Insecticide • Statistically higher insect catch in the fly bait equipment for nanogel formulation over ME alone • Lower fruitfly infestation of the fruits	Bhagat et al. (2013)

for pest/pathogen of interest, protection from premature degradation, reduced pesticide dosage, and decreased human exposure to ensure environment prudence (Nair et al. 2010; Kah et al. 2013, 2014, 2016; Chhipa 2017; Huang et al. 2018). The nano-formulated pesticides exhibit improved pesticide efficacy with even low concentration of the active ingredient owing to their small size (metastable state), high surface area to volume ratios, and low surface/interfacial tension which ensures greater wetting, spreading and thus higher penetrability or uptake of the a.i. by the test plant (Kah et al. 2013).

The nano-pesticides which aim for slow/controlled and targeted release profiles may contain nanoparticles/-capsules/-spheres serving as nano-vehicles for loading of the a.i. These formulations, thus, include amorphous, porous, or layered inorganic nonmetal oxide (silica and layered clay minerals) particles in nanoscale. However, the a.i. can also be embedded or encapsulated in synthetic or natural organic polymers for slow/targeted release (Kah and Hofmann 2014; Nuruzzaman et al. 2016). The polymers for the latter can be selected or designed to exhibit sensitivity to an array of abiotic and biotic components such as light, temperature, humidity, pH, and the presence or absence of a biological macromolecule(s) (such as enzyme protein) (Huang et al. 2018). The solubility and efficiency of pesticides developed as nano-emulsions (single or double oil-in-water emulsions) by acoustic cavitation or high-pressure homogenization techniques get enhanced manyfold compared to the conventional pesticides (Chhipa 2017). Interestingly, novel formulations of nano-pesticides can also possess the self-scavenging properties such as photocatalytic degradation of the pesticide a.i. or its residue through specific metal/metal oxide NPs incorporated in the formulation once the pesticidal action is not desired (Herrmann and Guillard 2000; Xue et al. 2014). The various nano-pesticides prepared and utilized for curbing the pests/pathogens of fruit crops are being given in Table 14.3.

14.3.3 Nano-Diagnostics: Nano-Enabled Sensor Technologies for Early Detection of Disease Pathogens and Pests

Nano-science inspired innovative sensing/tracking devices offering low-cost, quick, sensitive, and many-a-times real-time information on the chemical and microbiological status of the packaged food can be effective handy tools for tracking/tracing of the packaged food consignments (Kalia and Parshad 2015). The on-farm or real-time sensing devices, portable, miniaturized structures that can efficiently sense the occurrence and/or amount of certain chemicals/compounds/materials/entities are termed as ‘sensors’ (Jianrong et al. 2004). The sensor is comprised of three components: sensing element to selectively detect target in matrix, transducer to convert sensing element–target interaction to some measurable signal, and readout component to display digitally the quantity of the sensed target.

If nanomaterials are utilized for the fabrication of any of the components of the sensor, nano-sensor can be developed (Warriner et al. 2014). However, the sensors which utilize bio-receptor molecules such as proteins, enzymes, nucleic acids, and other macromolecules are termed as 'biosensor' systems. Inclusion of a nano-component (such as gold, silver, or other NPs) introduced to the bio-receptor or transducer entities of the biosensor system forms a 'nano-biosensor' (Rai et al. 2012). These biological moieties offer significantly improved selectivity, speed, and sensitivity compared to traditional chemical and biological methods (Omanović and Maksimović 2016).

Use of nano-enabled systems for development of point-of-care (POC) diagnostic devices involved in quick and early detection of pest/pathogen attacks in fruit crops are need of the hour (Kwak et al. 2017). These POC devices work on potentially diverse nanomaterials, principles as well as biogenic compounds/molecules (Coupland et al. 2010; Khiyami et al. 2014; Fang and Ramasamy 2015; Lau and Botella 2017). The nanomaterials that have been utilized for the fabrication of various types of POCs include metal NPs (Au, Ag, Au/Ag hybrids), metal oxide NPs (TiO_2, ZnO, CuO, CdSe/CdTe Q-dots), nonmetal oxide NPs (SiO_2, Al_2O_3), and carbon nanomaterials (Carbon Q-dots, Carbon nanotubes, carbon nanofibers, graphene oxide) (Fang and Ramasamy, 2015).

The nanomaterials can be utilized to fabricate both direct and indirect POCs having applications for plant disease diagnosis, temporal physiological disorders, particularly of the leaf tissues in response to stress and for determination of the freshness of the fruits (Coupland et al. 2010). The former includes one of the most easy to use portable, commercial 'electronic nose' POC devices, available in diverse handheld configurations which can identify infected trees by sensing the airborne, low-molecular weight organic compounds (plant volatiles) formed in response to mechanical, pest and pathogen attack (Coupland et al. 2010; Skrzypczak et al. 2017). Among the direct POCs, lateral flow devices (LFDs) are the commercially successful, low-cost, rapid and single-step, immuno-assay-based systems to detect a variety of plant pathogens including plant viruses and other pathogens (Posthuma-Trumpie et al. 2009). In an attempt to identify the bacterial pathogen, *Candidatus Liberibacter asiaticus*, causative agent of Huanglongbing or citrus greening disease, the proteins of the secretory system (Sec-delivered effector 1 or SDE1) have been utilized as a marker in an immuno-assay for HLB infected trees (Pagliaccia et al. 2017). However, the plant volatiles emanated in response to this pathogen can provide very accurate and early detection of Huanglongbing disease before appearance of visual symptoms which is superior to even DNA-based RT-PCR detection (Aksenov et al. 2014).

Another exciting feature of the sensor technology is its possibilities to integrate all the individual components through satellite/Internet. Mostly, these involve dedicated autonomous and self-powered hardware and modeling-based software combos that include wireless sensor network system deployed throughout the field/orchard to provide a unique decision support platform to early detection of disease, issuing of the warning to the growers and possible preventive/remedial plans (Pérez-Expósito et al. 2017).

14.3.4 Safeguarding the Produce: Nano-Enabled Post-harvest Solutions

14.3.4.1 Nano-Packaging Modules: Enhancing Fruit Shelf Life

Urbanization has led to proliferative growth of the food packaging industry. This industry caters to the packaging needs of a variety of sister concerns/subsidiary industries such as the fresh-cut fruit and vegetables, ready-to-eat meals, instant food, precooked foods, and other enterprises concerned with improving the preservation of food for prolonged shelf life (Kalia and Gupta 2012, 2017). It is being refurbished through nano-interventions so that wastage of food besides packaging material waste can be prudently dealt with. The NT-enabled solutions include ENM amendments to improve the material (gas exchange, photo-optic, mechanical) properties as well as to fabricate active packaging solutions or both at the same time (Radusin et al. 2016; Hu et al. 2011). The packaging films are traditionally prepared from non-degradable synthetic polymers. However, NP supplementation of the polymer to fabricate polymer-NP hybrids alters several properties of the new product (Hu et al. 2011). Like, nano-ZnO-based LDPE (NZLDPE)-packaging helped to form low O_2 and high CO_2 environment during the packaging of peaches and resulted in to prevention of chilling injury (Li et al. 2017a, b). Similar results were obtained in the case of strawberry when nano-TiO_2-LDPE packaging was used (Li et al. 2016). The major research publications have been on incorporation of NPs to develop antimicrobial polymeric films which enhance and prolong the protective function of pristine food packaging material (Kalia and Parshad 2015). The surging environmental awareness and disposal problems of the used packaging material are steering researchers to develop alternative nanocomposite-based biodegradable packaging solutions (Kaur et al. 2016b).

The potential applications of nano-enabled processes and products have been best identified and realized in food industry in almost every segment of the sector, viz., food processing, packaging, and nutrient supplements (Duncan 2011). Within food industry, the largest share of the current/predicted market for NT-based products is in packaging applications (Kalia and Parshad 2015). These predicted trends have been translated as popular commercial food packaging products flaunting the willingness of the consumers for ‘out-of-food’ nanoproducts (Uysal Unalan et al. 2014). The food packaging products are predominated by the use of petroleum-based non-biodegradable materials or plastics as basic material which poses disposal problems (Othman 2014). Therefore, to meet the increasing demand for sustainability and environmental safety, research efforts have been directed toward development of biodegradable food packaging materials that could be completely mineralized besides can be degraded rapidly (Jayaramudu et al. 2013).

14.3.4.2 Antimicrobial Properties of Nano-Fillers

The inorganic nano-fillers comprised of metal or metal oxide NPs like gold, silver, iron, TiO_2, zinc oxide, copper oxide, magnesium oxide besides SiO_2, and carbon

Q-dots have been used as antimicrobial agents in food packaging (Uysal Unalan et al. 2014; Kalia and Parshad 2015; Carbone et al. 2016; Kaur and Kalia 2016; Kaur et al. 2016b). The antimicrobial properties are by virtue of generation of highly reactive oxygen species (ROS) toxic to pathogenic microorganisms. Fabrication of dual or multiple metal NPs further enhances the antimicrobial potential as well as spectrum (Vohra et al. 2006). Enhanced antimicrobial activity was observed for combined application of NPs of Ag, TiO_2 and CNTs against *E. coli* and *Bacillus cereus* spores (Krishna et al. 2005). Sometimes the packaging material with modified properties may not be feasible, and to extend the post-harvest quality of fruits, the coating on their surfaces is an effective alternative. In one study, nano-ZnO coatings of strawberry controlled multiplication of aerobic mesophilic bacteria and yeast and mold during the storage (Sogvar et al. 2016). When an edible coating of chitosan–alginate was applied on fresh-cut mangoes, it increased the self-life by 8 days (Souza et al. 2015).

14.3.4.3 Improvement of Mechanical Properties

Incorporation of nano-phase layered clay minerals in polymers is one among the most promising bionanocomposite (BNC) development strategy. Clay incorporation results in a significant reinforcement, and their relatively simple processability improves the tensile strength and gas barrier properties of the polymeric matrices (Kanmani and Rhim 2014; Barikloo and Ahmadi 2018). Moreover, clays occur naturally as these originate from the earth's crust, are abundant and thus, cost effective, and have high surface area and aspect ratios (Bruna et al. 2014). The increase in the tensile strength and modulus of BNCs besides decrease in elongation at break depends on the amount or quantity of the nano-filler added in BNCs (Tang et al. 2012). The altered BNC mechanical properties may be attributed to the greater rigidity of the nano-fillers as well as excellent affinity between biopolymer and nano-filler at the interface (Rhim et al. 2013). These interfacial interactions between polymer and nano-filler also improve the thermal properties of BNCs.

The supplementation of high aspect ratio layered clay minerals also improves the barrier properties for gases and water vapor. However, improvement in barrier properties depends on the types and quantity of nano-fillers used as well as the aspect ratio of the nano-fillers (Rhim et al. 2013). The improved gas barrier properties of BNCs have greater applications in food packaging owing to considerable shelf-life enhancement of the packaged food product. A packaging film prepared by mixing nanoclay with polyethylene (PE) has shown better performance during the storage of mature peach fruit by improving barrier properties of the film (Ebrahimi et al. 2018).

14.3.4.4 Sensor Technology: Knowing the Fruit Quality of Stored Fruits and Juices

Nano-sensors can be used for the determination of microbes (Kaittanis et al. 2006), contaminants (Ai et al. 2009), pollutants (Liu et al. 2010), and food freshness

(Pimtong-Ngam et al. 2007). The most common, low-cost, and robust nano-sensor assays exhibiting ease of observation involve visual color changes in metal/metal oxide/semiconductor (Ag/Au/Fe_3O_4/CdSe/CdTe/ZnS) NP sols in the presence of analyte(s), i.e., contain optical transducer systems (Jang and Hassibi 2009; Ang et al. 2016). Several variants of these optical nano-sensors such as surface plasmon resonance (SPR), fluorescence, fiber optic, and probes encapsulated by biologically localized embedding (PEBBLE) are available now. The commercialized nano-sensors are electrochemical sensors, miniaturized ion-sensitive field-effect transistor (ISFET), metal oxide semiconductor (MOS-FET), and potentiometric electronic nose or tongue (e-nose/e-tongue).

The glucose content of the fruits has gaining attentions for the diabetic patients, and a simple, reliable, and economical tool to measure glucose content of fruits is needed. In one study, an amperometric sensor with glucose oxidase (GOD) immobilized on chitosan membrane, and a platinum working electrode was developed. The results of the study have shown that a developed biosensor possesses good repeatability and reproducibility (Ang et al. 2015). Many different fruits contain vitamin C that has antioxidant properties. The determination of L-ascorbic acid content of fruit juices can provide the information regarding the antioxidant properties of the commercial preparations. To measure ascorbic acid in fruit juices, an amperometric ascorbate biosensor containing the ascorbate oxidase mounted over working electrode was developed. The biosensor has shown the properties like fast response time, repeatability, and long-term stability (Chauhan et al. 2010, 2011; Csiffáry et al. 2016; Wen et al. 2012).

In another study, an electrochemical enzymatic biosensor with electrodeposited Au nanoparticles and laccase was developed for quantification of the formetanate hydrochloride (FMT) pesticide in fruits (Ribeiro et al. 2014). The results of the study had indicated that the biosensor fulfill the criteria of sensitivity, accuracy, repeatability, stability and can be used for establishing the presence of FMT in fruits. The bi-enzymatic biosensor was successfully used to quantify carbamates in fruits (Oliveira et al. 2014). Use of such biosensors for quality monitoring in the fruit industry can have an economical as well as health benefits to consumers.

14.4 Safety Concerns

As engineered nanomaterials are known to possess unique alternative properties, there are enormous possibilities of interactions with the components of the dynamic soil system in a myriad of manner. Thus, ENMs are speculated to have variable solubility, extent/amount of bioavailability, transformation kinetics, and transportation mechanisms in comparison with their elemental bulk forms. Moreover, the lack of physical methodologies for prediction of potential impact of ENMs on both environment and human health is critical (Ke and Lamm 2011; Salonen et al. 2016). The direct and intentional application of nano-agrochemicals in the environment will be critical owing to their pronounced anticipated environmental impacts (Kah et al. 2013). The public concerns are also impeding the rush-in of commercialized NT-based products and devices. Moreover, as agriculture is a low-profit industry, high cost of the ENM-formulation-based agrochemicals is the real hitch (Kah 2015). The public acceptance of the technology is further cluttered down due to a high risk of rejection by the environment and health regulatory bodies worldwide (Kah and Hofmann 2014).

14.5 Future Prospects: Where the 'Nano' Go Will Go?

The consumer marketplace has now been sufficiently penetrated by the nanotechnology-derived products/devices as the two agencies: Woodrow Wilson International Center for Scholars and the Project on Emerging Nanotechnology have documented and listed 622 companies across 32 countries manufacturing 1814 consumer products (Vance et al. 2015). However, in spite of enormous interest in R&D and substantial pervasiveness of the nanomaterial-based commercial products, there are still no specific provisions or regulatory governing agency(ies) to deal with the evaluation and certification of commercial products containing nanomaterials. The nanotechnology R&D prima foci, both USA and European Union, deal with nanomaterials or products derived from them along with other hazardous chemicals and pesticides under the EPA's Toxic Substances Control Act (TSCA) or the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for the former and Concerning the Registration, Evaluation, Authorization and Restriction of Chemicals or Classification, Labeling, and Packaging for hazardous chemical substances (pesticides) and Biocidal Products Regulation (nano-silver and similar formulations) and European Commission (cosmetics products containing nano-TiO_2) for the latter (Vance et al. 2015). Therefore, efforts such as documentation of the nanoproducts have to unfurl globally particularly in the developing nations in Asia, Middle East and underdeveloped countries in the sub-Saharan/African continent.

14.6 Conclusion

The science and technology of nanoscale offers an exciting scientific frontier. With the advancements in the tools and techniques to characterize and synthesize ENMs, our capabilities of observation, manipulation, and generation of materials at a scale dimension of 1–100 nm possessing novel properties have been tremendously enhanced. A range of ENM/ENP-based products and devices are being developed which are finding apt applications in diverse fields of agriculture and food industries. However, the Janus face of nanotechnology sways between the possible environmental-friendly supremacy of NT-based technologies and the anticipated intentional niche contamination and related health hazards. Therefore, addressing the critical balance desired to exploit advantages while avoiding unidentified harms.

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Chapter 15
Nanomaterials and Vegetable Crops: Realizing the Concept of Sustainable Production

Anu Kalia and Sat Pal Sharma

Abstract Sustainability refers to a multi-dimensional integrative approach for any production system to achieve growth targets while managing the inputs and outputs prudently. This aspect holds its new promise for agriculture, particularly the vegetable production systems which are run as marginal or medium-scale operations. Hence, these cannot afford a piecemeal approach to maintain productivity standards over longtime. Nanotechnology interventions for vegetable production and protection can assure improved productivity with low inputs, enhanced input use efficiency, precision application through quick diagnosis of the pest/pathogen attack, and by curbing non-target losses that may lead to environmental contamination and hazards. In spite of the great promise of nanoproducts and nanodevices, the requirement of bulk quantity under field conditions (particularly for nanofertilizers and nanopesticides) and the economic cost of production (of nanosensors for pest/pathogen diagnostics) are substantially high. However, these issues of nanoagri-products can be off-set through scaled-up production using improved manufacturing technologies. Further, the stigmatization of the nanoagri-ventures to follow the socio-psychological fate similar to genetically modified crops is also required to be effectively dealt with firm efforts from agri-nanoresearchers. This discipline is in its incipient stage, but it holds promise for enhanced productivity with less depletion of the resources and maintenance of ecological sanctity.

Keywords Agri-nanotechnology · IOT · Nanoagri-inputs · Nanosensors · Sustainable production · Vegetable crops

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15.1 Introduction

The wholesome concept of sustainable agriculture production envisions achieving enhanced yield of high-quality produce for improving livestock and human health without any environmental penalty. Tremendous research and development strategies have been developed, evaluated, and implemented for the realization of this concept. However, none of the developed strategies singularly or in combinations could fulfill it completely or even partially accomplish the goals probably due to inability of meeting the production standards desirable for satiating the demand of burgeoning human population. Likewise, technological efforts will be worthwhile for not only increasing productivity per unit land but also will be useful for improving produce quality. Therefore, technologies mimicking sustainable agricultural systems will be prudent for ensuring nutritional security to the masses and preventing environmental degradation through input-intensive systems.

15.1.1 What is Sustainable Agriculture?

Agricultural sustainability invariably reflects environmentalism involving indefinite continuation for the ability to maintain the rate of depletion of the non-renewable resource, harvest of the renewable resource, and pollution creation (Pretty 2008). Sustainable agriculture production can only be achieved through acquisition of a balance among the triad components: economic vitality, environmental rationality, and social equity (Velten et al. 2015). The major threats for realization of the concept of sustainable agricultural production pertain to degradation of the arable lands, loss of soil microfloral and faunal diversity (Thrupp 2000; Pretty 2008), squeezing of water resources, and escalating cost of production due to low input use efficiency (Velten et al. 2015).

Land degradation due to ‘industrial agriculture’ is the most prominent cause for land under vegetable cultivation which invariably intimidates long-term sustainability concept as the common agricultural practices of land preparation and vegetable production involve heavy tilling, and abundant and inefficient use of agrochemicals to obtain multiple harvests per unit land and time (Juroszek et al. 2008; Bhattacharyya et al. 2015; DeLong et al. 2015). Degradation of the land already under active agriculture and rapid urbanization have led to escalated intrusion of land masses under forest cover for agriculture purpose, i.e., increased ‘agriculture footprint’ leading to grave environmental consequences (Foley 2011). Further, the human resource component accountable for land-farming is dwindling particularly it has sizeable significance for the agri-economy centric developing nations as probably the under-privileged, poverty stricken rural population cannot maintain high farm-outputs and hence, the economic viability of the farm operations (Hayati et al. 2011).

Vegetable farming is highly labor-intensive enterprise and holds a comparative advantage for developing or under-developed nations as there is abundant labor to work on scarce land resources (32–34 laborers per hectare per day) (Dastagiri et al. 2013). However, without capital investment on processes of soil conservation and corrective measures for replenishment of the lost fertility of the soil, the labor-led intensification is unlikely to favor sustainable production (Hunde 2017). Moreover, the human resource-related agri-sustainability aspects are also emerging for the food habits (Sabaté and Soret 2014). The preference for low environment taxing plant-based vegetarian diets over the high input requiring non-vegetarian diet bears significant environment suitability (Marlow et al. 2009). Therefore, agri-systems aiming for most appropriate utilization of products and processes of environment without damaging these assets qualify for superior sustainability (Pretty 2008).

15.1.2 How to Achieve Sustainable Vegetable Production? —What Has Been Done so Far?

As discussed earlier, sustainable vegetable production should mandate comprehensive nutrient, pest, and disease management utilizing strategies involved in integration of several naturally operating biological and ecological processes resulting in minimum resource depletion and enhanced reliance on agri-know-how (Juroszek et al. 2008; Dwivedi et al. 2017) (Fig. 15.1). Thus, the industries based on horticulture are aiming for food security and provision of healthy diet by maintenance and conservation of their resource base as well as the environment through efforts to curb adverse effects on soil productivity and environment quality, thereby repairing the effects of past practices of industrial agriculture model to meet the present and future demands (Juroszek et al. 2008).

Materialization of sustainable vegetable production (Phatak 1992) has been accomplished through integrated use of improved varieties/hybrids exhibiting higher pest and pathogen resistance/tolerance to abiotic stresses besides having better yield under resource-poor conditions (Fess et al. 2011; Shelton and Tracy 2016; Tamilselvi and Arumugam 2017), application of optimum dosage of inorganic nutrient fertilizers in combination with biofertilizer and organic residues such as manure/compost incorporations (integrated nutrient management) (Bello 2008; Pandey and Chandra 2013; Stavi et al. 2016), better pest management strategies to decrease the use of pesticides (Meerman et al. 1996; Xu et al. 2008; Pretty and Bharucha 2015), and utilization of less energy-intensive cultivation tools and techniques. An improved end-use quality of the produce through vegetable breeding and/or management strategies has ensured higher phytochemicals, bio-active compounds, vitamins, and mineral-fortified vegetable produce (Miller and Welch 2013; Vanderschuren et al. 2013; Alshaal and El-Ramady 2017; Bouis and Saltzman 2017). As a sustainable system involves both food security and quality, it holds greater relevance to the marginal and resource-poor growers who can ensure quality food in remote areas, particularly those which lack access network for outside food sources as well as the necessary agri-inputs (Beckford et al. 2011; Kpéra et al. 2017).

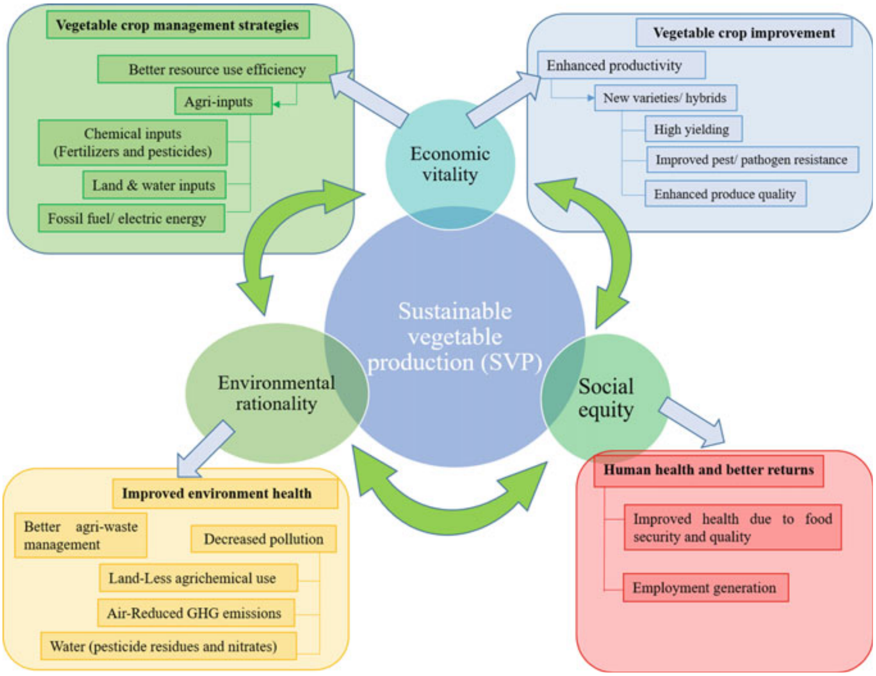

Fig. 15.1 Triad of sustainable vegetable production and the strategies to achieve food security, quality, and safety

However, products and technologies for sustainable vegetable production are still under development to match up the production standards and economic vitality of industrial agricultural practices (Dennis et al. 2010). Moreover, the seasonality and profound perishability components of vegetable produce demand a synergism among multifarious strategies for production vis-à-vis marketing to overcome and better address both shortage and glut issues (Juroszek et al. 2008). Further, creation of awareness among the vegetable growers for the market-oriented farming will fetch premium prices for the produce besides the economic resilience by producing specialized/elite vegetables (Bala et al. 2011; Schreinemachers et al. 2018).

As discussed in Sect. 15.1.1, being a labor-intensive enterprise, vegetable production can provide more employment per hectare (average 297 labor days per hectare per season) compared to labor employed for cereal crop cultivation (116 labor days per hectare per season), particularly for the dwellers of the Asian countries (Schreinemachers et al. 2018). Additionally, it does not require big farm holdings and very heavy farm-mechanization; rather it can be easily adopted by technology-savvy small farm operation holders ensuring high remunerations in short time periods (Subba Rao and Reddy 2006; Bala et al. 2011; Schreinemachers et al. 2018). Therefore, the higher production and export of the surplus vegetables besides the mushrooming of the post-harvest and processing-related enterprises has been a part of the Asian agri-economy.

Being the second largest producer of fruit and vegetables, India has a significant presence in the world market as exporter of specialized horticultural commodities particularly grapes, banana, and mango (fruit crops) and peas and potatoes (vegetables) (Ramesh et al. 2017). According to the annual report (2017) of National Horticulture Board (NHB), India, the vegetable production of the country has been escalated from 58.5 to 175.0 million tonnes during the last 1.7 decade spanning over from 1991–1992 to 2016–2017 (http://nhb.gov.in). The raising reforms, R&D, and technology dissemination in horticulture sector have led to a corresponding increase in average yield of vegetables from 10.47 to 17.01 MT ha^{-1} for the same period (http://nhb.gov.in). Likewise, as per the provisional estimate published in NHB report (2017), the area under vegetable cultivation in India has also expanded ($\sim$10.29 million hectares in 2016–2017) but has still been dominated by the marginal, small, and semi-medium operational holdings as per the Agriculture Census in 2011. Therefore, the innovative technologies which can efficiently address the problems and prospects of these vegetable growers can sufficiently lead for ensuring sustainable production and nano-enabled technologies can provide the possible solutions.

15.2 Nanomaterials: Properties and Applications

Sustainable vegetable production systems (SVPS) aim for the better resource use efficiency, decreased cost of production through less application of agri-chemicals, and environment prudence. The nanotechnology products and processes are anticipated to ensure enhancement of the benefits of SVPS. The proceeding sections elaborately deal with nano-interventions for improved yield, quality, and safety of the vegetable crops.

Nanomaterials are any nanostructured entity, viz., nanoparticles, nanoclusters, nanocrystallites, and nanograins, having size in the range of 1–100 nm (Buzea et al. 2007; Lovestam et al. 2010). These materials can have diverse composition spanning over composites, compounds, alloys, or elemental solids (Sun 2007). The physical (Lue 2007), chemical (Schwirn et al. 2014), and biological interaction properties (Dobrovolskaia et al. 2007) of these materials digress from their bulk counterparts (Christian 2009) and mostly depend and thus vary according to the morphology, surface properties, and chemical composition of the nanomaterial (Subbenaik 2016). These can exist as aerosols, powders, emulsions, suspensions, or dispersions. Nanoformulations, stable liquid suspension of NMs particularly nanoparticles (NPs), are the most utilizable form of the nanomaterials and already have been used extensively in pharmaceutical and personal care products (Ochubiojo et al. 2012; Lohani et al. 2014; Zhang et al. 2015b). The use of this term in agriculture is recent and largely involves the application of nanoparticle suspensions, 'nanosols' for varied purposes.

Nanoformulations of the materials can be generated by two basic approaches: (i) top-down and (ii) bottom-up techniques by following the three basic methods, i.e., physical, chemical, and biological syntheses (Tulinski and Jurczyk 2017). The physical techniques are useful to synthesize NPs at a mass scale in good quantities, while the chemical processes can be instrumental in obtaining homogenous-sized NPs (Roduner 2009). However, discussion on all these synthesis techniques is beyond the scope of this manuscript. The third technique for the synthesis, the biological synthesis, is most economical. The utilization of cell-free extracts of living tissues/cells for generation of nanomaterials from dissolved ionic forms of the metal/metalloid salts holds a great promise as biogenically developed NPs can be of any possible shape (mimicking the morphology of the biotemplate utilized) and present good polydispersity, dimensions, and stability (Mittal et al. 2013; Husen and Siddiqi 2014). The basic mechanism of the biological synthesis is bioreduction due to presence of diverse primary and secondary biomacromolecules present in the cell-free extracts. Both pro- and eukaryotic cell extracts have the potential for nanoparticle generation, and bacterial (Li et al. 2011), fungal (Rai et al. 2015), algal (Korbekandi and Iravani 2013), and plant (Husen and Siddiqi 2014) cell types have already been evaluated for their nanoparticle synthesis potential (Shah et al. 2015).

The plant-based ‘phyto-synthesis’ or ‘phyto-fabrication’ of various nanoparticles presents an articulate, economically viable and scalable technique (Husen and Siddiqi 2014). Phyto-mining is an inherent characteristic of certain plants as their roots forage, adsorb, uptake, and accumulate elements from soil and may even lead to synthesis of nanomaterials inside the plant tissues (Marchiol 2012). Phyto-fabrication depends on the occurrence or absence of specific phyto-reductants, their relative concentrations, and plant secretome (Shah et al. 2015) in plant extract that can affect the morphology and thus properties of the synthesized nanoparticles (Mittal et al. 2013). Nanoparticle synthesis through this approach is readily scalable and takes relatively short production periods for lower generation costs compared to other biological systems (Kharissova et al. 2013; Jeevanandam et al. 2018).

Nanomaterials exhibit unique properties which are not observed in their bulk material (de Voorde et al. 2017). The novel properties of nanomaterials can be summarized to arise due to size-dependent effects dichotomized as quantum effects and occurrence of fraction of surface or interfacial atoms possessing extremely large specific surface area (Roduner 2006). These two characteristics can ensure tailoring of several nanomaterial properties, viz., chemical catalysis, and mechanical (high strength, toughness, ductility, formidability, superplasticity) (Guo et al. 2014), optical (variable light-nanomaterial interactions), electrical (Tsujimoto et al. 2015), and magnetic properties (Roduner and Jensen 2015) due to size dependence (Lue 2007; Sun 2007; Christian 2009). In other words, the nanomaterials exhibit confinement of electrons to a rather small volume, variable interatomic interactions, and fraction of the under-coordinated atoms which invariably dictate their aberrancy from individual atom or bulk state of the same material (Sun 2007; Biener et al. 2009). Therefore, the properties of nanosolids are morphology-dependent i.e. size and shape specific.

Nanomaterials due to their size- and shape-dependent tunable properties have enormous applications in diverse industries such as photonics, paint, ceramics, pharmaceuticals, cosmeceuticals, pollution remediation, water purification, and electronics (Aitken et al. 2006; Zhang et al. 2015b). The nanoproducts commercialized so far have utilized the increased antimicrobial potential, super-hydrophobicity, thermal resistance, targeted and controlled delivery of active ingredient (could be drug, nutraceutical, cosmeceutical moiety), and band-gap opto-electrical properties (Wijnhoven et al. 2009; Shatkin et al. 2014). The rapid commercialization and availability of products have thus, led to creation of registry system for the monitoring of the nanoproducts (Bergeson and Mihova 2014).

15.3 Nanomaterials and Vegetable Crops

The agricultural and particularly the horticultural applications of nanomaterials are still in their incipient stage and are largely restricted to proof-of-concepts/models led by research and development teams of both public and private giants across globe. A lot of governmental initiatives started with the model initiative in the year 2000 in USA (National Nanotechnology Initiative) which has followed a long path with more than 60 countries including Germany (Europe), Asian giant China, Japan as well as India (Nanoscience Mission under auspices of Department of Science and Technology, GoI) besides Israel and Iran to fuel funds for research in nanotechnology (Dong et al. 2016). Nonetheless, the applications are plenty, and there are enormous possibilities for the realization of nanorevolution in vegetable production, protection, and processing arenas.

Nanomaterials can have multi-faceted role for improving vegetable production through use of innovative slow/controlled and even targeted release nanofertilizers (Liu and Lal 2016), effective crop pest management with nanopesticides (Kah and Hofmann 2014; Kah et al. 2018a), and point-of-care nanodevices for rapid and sensitive detection of pest or pathogen presence or damage to the crop (Martinelli et al. 2016).

15.3.1 New-Age Fertilizers: Curbing the Nutrient Losses for Enhanced Vegetable Production

Nanofertilizers are important tools in agriculture that can improve crop growth, yield, and quality characteristics. These novel fertilizers exhibit better nutrient use efficiency, thereby helping in reducing wastage of the applied fertilizers, and thus decreasing the cost of environment protection as well as crop cultivation (Singh et al. 2017). These alternative fertilizers have nutrient fertilizer element in its either nanostructured state or pay-loaded on a nanoscale delivery vehicle (Kalia and Kaur 2019). Such nanoscale existence of the nutrient element results in controlled release of the nutrient through dissolution and ion exchange rendering efficient uptake by the plant roots without incurring substantial losses (Monreal et al. 2016). Therefore, these fertilizers are one of the adjunct technologies in precision agriculture which aim at controlled and targeted delivery of the nutrient in accordance to the crop growth stage and may provide nutrient throughout the crop growth period (Naderi and Danesh-Shahraki 2013; Kalia and Kaur 2019). Interestingly, non-nutrient engineered nanomaterials can also be considered nanofertilizers provided their application alters the host-plant metabolism, thereby increasing photosynthetic rate, biomass accumulation, and finally the yield.

Nanofertilizers can be applied through several routes, viz., soil, foliar, seed priming/dressing, seedling root dip, fertigation through drip tape, and aerosol dusting (Kalia and Kaur 2019). The utility of the nanofertilizers lies in being more use efficient, i.e., increased availability to the crop plant due to curbing of the ecological non-target losses incurred through volatilization, leaching, runoff and microbial transformation, and mineralization processes (Kah 2015; Kah et al. 2018a). The release of nutrient in plant-available forms from nanofertilizer(s) is most likely to have great implications for vegetable crops which generally possess shallow root systems and also exhibit heavy nutritional demands. The mode of application of the developed nanofertilizers also have to be customized for different vegetable crops due to enormous diversity for the duration of the crop and the method of planting, i.e., direct seeded or seedling transplanted vegetable crops. Nanopriming and coating of seed surface with nanoparticles can improve the percent seed germination and seedling vigor and establishment (Maroufi et al. 2011). However, an innovative approach of electrospray deposition of metal oxide nanoparticles for very brief periods of 2–4 min only can induce similar or even improved effects as observed in nanopriming or seed coating experiments (Wu et al. 2014).

Nanoscale fertilizers can be developed for both macro- and micronutrients (Chhipa 2017). As discussed earlier, nanoscale fertilizers can be developed through top-down and bottom-up approaches. However, it is improbable that all types of NFs can be synthesized through one or both techniques as in-depth understanding to probe chemical nanothermodynamics of interacting reactants, products, and interfacial interactions of the constituent nanostructures is prerequisite (Kalia and Kaur 2019). The most referenced, economically feasible top-down approach for the synthesis of nanonutrient fertilizers is attrition or mechanical grinding, a physical technique which has been utilized for generation of clay-mineral-based (Kottegoda et al. 2011) or apatite-based nitrogen nanofertilizer products (Kottegoda et al. 2017). The bottom-up techniques for nanofertilizer synthesis primarily involve chemical precipitation or phase separation techniques while the recent trend is gaining impetus for biological or green synthesis of various nanomaterials, for instance, the micronutrient metal/metal oxide nanoparticles particularly due to the associated low-cost and environment-safety benefits (Husen and Siddiqi 2014; Raliya et al. 2014; Palmqvist 2017).

The macronutrient fertilizers applied for vegetable cultivation include nitrogen (urea, calcium ammonium nitrate as basal dose), phosphorus (single superphosphate, diammonium phosphate as basal dose), potassium (muriate of potash, potassium nitrate as basal dose), sulfur (calcium sulfate or gypsum, ammonium sulfate, potassium sulfate, potassium, and magnesium sulfate as basal dose particularly for cole crops and onion and garlic), and magnesium (magnesium sulfate as foliar application) fertilizers. However, these conventional inorganic/synthetic fertilizers exhibit huge losses on application, particularly the use efficiency is substantially low for nitrogenous and phosphatic fertilizers (Herrera et al. 2016). Therefore, development of nano-N and nano-P fertilizers will be most appropriate as vegetable crops exhibit huge demand for these nutrients. The controlled/slow release of these nutrients can be ensured by either encapsulating the nutrient in polymeric matrix (both synthetic and natural polymers such as chitosan, polyvinyl alcohol, starch, alginate, polyethylene glycol, carboxy methyl cellulose, and many more) (Jarosiewicz and Tomaszewska 2003; Corradini et al. 2010; Rashidzadeh and Olad 2014; Pereira et al. 2015; Giroto et al. 2017), sequestering it in porous nanovehicles such as layered double hydroxides (LDHs), silicate minerals (Roshanravan et al. 2015; Sempeho et al. 2015), silica nanoparticles, and adsorption on metallic or non-metallic NPs (nanohydroxyapatite)/carbon nanomaterials (Milani et al. 2015; Yatim et al. 2015; Giroto et al. 2017). These interventions will ensure gradual nutrient release from the polymeric/porous matrix that may better coincide with plant nutritional demands, thereby minimizing non-target losses due to leaching and will improve the fertilizer use efficiency (Madhavi et al. 2016). The nano-P fertilizers on the contrary can help in enhancing plant available-P by decreasing the P-retention from sources such as rock phosphates for about one-month period (Devnita et al. 2018). Development of nanofertilizer as liquid or encapsulated suspensions also offers for balanced fertilization due to multiple nutrient loadings such as essential triple elements along with necessary micronutrients such as Zn, Mn, and Fe (Subramanian et al. 2015; Valizadeh and Milic 2016; Giroto et al. 2017).

Vegetable crops exhibit typical micronutrient deficiency disorders, thereby decreasing the plant biomass leading to yield penalty and many a times death of the crop plant (Chatterjee and Dube 2004). The antecedents of micronutrient deficiency have increased over the past four decades as the agricultural soils have become impoverished of the essential micronutrients as a legacy of the post green-revolution era (Pingali 2012). Industrial agriculture has led to unsustainable and inherently leaky cultivation systems (Jones et al. 2013). Moreover, the rising atmospheric carbon dioxide concentrations (greenhouse gas) have further complicated the micronutrient deficiency syndrome as the C_3 plants (cereal grains crops such as rice and wheat) grown under elevated CO_2 concentrations can accumulate only lower micronutrient contents (Smith et al. 2017). This may commensurate to deficiency in humans and livestock and has initiated hunt for possible alternatives. Vegetables can be the most probable option particularly for the Asian and sub-Saharan countries to address and correct micronutrient deficiencies (Ali and Tsou 1997).

Improvement of the essential micronutrient contents in vegetables can further be effectively achieved through development of micronutrient nanofertilizers (Dimkpa and Bindraban 2018; Kalia and Kaur 2019). These fertilizers can effectively address the basic problems of conventional micronutrient fertilizers, i.e., fixation or precipitation of the applied fertilizers and conversion to plant unavailable forms on application in neutral to calcareous soils. As most of the trace elements exhibit slow mobility through plant tissues, nanoscaling the nutrient element may ensure easy internalization in the plant tissues through natural openings or from wounded regions due to its occurrence in non-ionic form (Raliya et al. 2017). Furthermore, the micronutrient nanofertilizers are expected to affect the relative distribution or assimilation of the supplied nutrients throughout the plant body through acropetal and basipetal translocation after active/passive uptake on soil and foliar application, respectively (White 2011a, b). However, unlike the macronutrients, particularly nitrogen, phosphorus, and potassium, bulk applied state micronutrients seldom travel basipetally leading to low micronutrient levels in root tissues, specifically in crops grown in neutral soils (Wang et al. 2012). This may cause lowering of plant immunity for root-specific pathogenic attacks. Nanomicronutrient fertilizers can effectively avert this bottleneck of the traditional micronutrient fertilizers as the foliar-applied nanoparticles travel through the apo- and symplast channels to reach the vascular stele and later to the root system (Wang et al. 2012). This attribute of nanomicronutrient fertilizers is anticipated to help in enhancing the immunity of the test crop and will ensure higher yield. Moreover, the application of nanomicronutrients can also improve the use efficiency of nutrients applied as inorganic/synthetic NPK and other fertilizers (Kale and Gawade 2016).

15.3.1.1 Effect of Nanofertilizers on Vegetative Growth, Yield, and Yield Attributing Characters and Tolerance to Abiotic/Biotic Stresses

Vegetable crops exhibit voracious nutrient mining and uptake from soil due to their fast and high biomass accumulation potential. Therefore, nutrients are required in high amounts and in plant-available forms in upper few inches of the soil strata. As discussed in above section, the positive effects of application of nanoscale fertilizer nutrient depend largely on occurrence in plant-available form besides protection from various losses. The morphology and chemical nature of the nanoscaled nutrient will affect its dissolution rates in soil solution, and its fate or the journey from the site of application (Liu and Lal 2016). The soil microbes particularly the rhizospheric microflora may interact with the applied nanomaterials and can further affect its effects. For instance, co-application of nanorock phosphate particles in soil with biofertilizer PSB resulted in decreasing the soil pH and organic carbon (OC) contents which will have further implications (Arifin et al. 2018).

Other than nutritional sufficiency creating nanomaterials, certain non-nutritional nanomaterials may also exhibit plant-promotional properties which can be attributed to their ability to interact with a myriad of biological components of the cell/tissue on application. Majority research reports indicate a concentration dependent bio-effects of various types of nanomaterials which sway from positive, negligible to negative impacts (Yang et al. 2015; Zhang et al. 2015a; Pestovsky and Martínez-Antonio 2017; Siddiqi and Husen 2017; Xiong et al. 2017). Thus, applications of lower or sub-optimum concentrations of nanomaterials can promote vegetative growth of plants probably through enhancement of diverse components of the photosynthetic system, i.e., increased chloroplast number per cell, higher thylakoid or granal stacks per chloroplast, improved photosynthetically active radiation (PAR) harvesting, and alterations in the leaf organizations (Yuan et al. 2018). The mode of application of the nanomaterials may also affect the fate of the applied nanomaterials for example, occurrence of organic components (humic and fulvic acids), inorganic clay crystals, plant root exudates, the soil microbial flora of the rhizosphere and soil water content can alter the effective concentration and availability of the soil applied nanomaterials (Liu and Lal 2015). Thus, most of the studies have evaluated the role of foliar-applied nanomaterials. The published reports on nanofertilizers and their effect on growth and yield of various vegetable crops have been summarized in Table 15.1.

15.3.1.2 Augmented Bio- and/or Nanopriming of the Seeds: Modulating the Action Spectrum of Biofertilizers for Improved Growth and Yield of Vegetable Crops

The improvement in the growth and yield in vegetable crops by application of nanomaterials has already been discussed in detail. Likewise, the inoculation or seed bio-priming with plant growth promoting rhizomicrobes (PGPRMs) has a great role in sustainable agriculture (Lutts et al. 2016; Mahmood et al. 2016; O'Callaghan 2016) and particularly vegetable cultivation (Kalia et al. 2016). Even the seed spermosphere is comprised of diverse surface and endophytic microbial genera which may significantly affect the survival potential of the test plant due to enhanced endurance for combating various abiotic/biotic stresses (Vujanovic and Germida 2017). To reap the dual benefits of nano- and bio-agent application in crop plants, a converging discipline of applied technology is emerging as 'bio-nanopriming.'

The nanomaterials exhibit three-way interactions with plant, beneficial PGPRMs, and the soil components. Exposing PGPRMs with metal or metal oxide nanoparticles may lead to alteration in their secondary metabolite and protein synthesis profiles in a dose-dependent manner (Haris and Ahmad 2017). On exposure of microbial cells in liquid broth conditions with metal/metal oxide or carbon nanomaterials at sub-lethal low concentrations, programs enhanced production of the secondary metabolites such as phytohormones (indole acetic acid) (Dimkpa et al. 2012) and metal-chelating ligands such as siderophores (Oves et al. 2014; Poiata and Creanga 2015) will occur that may modulate the PGP benefits in test plants on co-immobilization/coating of the crop seed (Timmusk et al. 2018). The bio-nanopriming strategies may include co-application of nanomaterial and PGPRM on seed (Timmusk et al. 2018), treating seed surface with beneficial PGPRMs immobilized on nanomaterial matrix (De Gregorio et al. 2017; Firmansyah et al. 2017), treating the seed surface with beneficial PGPRM(s) or its bio-active molecules such as microbial cyclo-peptides, known as bio-priming

Table 15.1 Nanomaterials evaluated for nutrient delivery and other beneficial effects in vegetable crops

Nanofertilizer evaluated	Size dimensions/ other characteristics	Test concentrations	Mode of application	Test vegetable crop	Study conditions	Traits evaluated or affected			Stress toler-ance	References
						Vegetative	Yield attributing and yield	Quality attributing		
Macronutrient nanofertilizers										
Nitrogen	Nano-N chelate: 20–22 nm, Nano-N chelated sulfur: 44.07–83.89 nm	Three doses (L ha^{-1}) of NNC: 127, 255, and 383, SNNC: 127, 255, 383	Broadcasting at two stages, i.e., at planting and at flowering time	Potato (*Solanum tuberosum* L.)	Greenhouse study	–	High yield: SNNC (@ 250 L ha^{-1}), NNC (@ 383 L ha^{-1}) compared to 300 kg ha^{-1} urea (31.05 ton ha^{-1})	–	–	Abyaneh and Varkeshi (2014)
Phosphorus	Mean particle diameter of 15–24 nm	Nanohydroxyapatite particles @200 mg P kg^{-1} soil	Basal soil application	Lettuce (*Lactuca sativa* L.)	Pot experiment	Numerically higher growth and dry biomass	Higher P content in high calcareous soil	–	–	Taşkın et al. (2018)
Sulfur	Average diameter 20–80 nm	0–600 ppm	Seed soaking in SNP aqueous suspension	Cucumber (*Cucumis sativus* L.)	In vitro study	Statistically significant germination and root and shoot growth	–	–	–	Albanna et al. (2016)
	Mean size 5–80 nm	100–600 ppm doses	Applied to the field soil	Summer squash (*Cucurbita pepo*)	Field study	SNPs increased number of leaves and branches, plant height, stem diameter,	–	–	–	Salem et al. (2015)
Calcium	–	Lithovit (Lith) at 500 mg L^{-1} (with and without boron)	Foliar spray at early morning (20 L) to runoff twice, at 50 and 60 days from planting	Potato (*Solanum tuberosum* L. cv Spunta)	Farm study	Significantly higher plant height, branch number/plant, shoot fresh and dry weights and leaves area per plant n lithovit over control	Higher yield	Highest starch and soluble sugars in Lithovit + Boron	–	Farouk (2015)

(continued)

Table 15.1 (continued)

Nanofertilizer evaluated	Size dimensions/ other characteristics	Test concentrations	Mode of application	Test vegetable crop	Study conditions	Traits evaluated or affected			Stress toler-ance	References
						Vegetative	Yield attributing and yield	Quality attributing		
NPK	–	Nanonat and Ferbanat @ 0, 2.0, 3.0 and 4.0 L ha^{-1}	Foliar sprays at ten days interval three times during plant growth, beginning two weeks after transplanting	Cucumber (*Cucumis sativus* L. cv. A-21F1)	Greenhouse study	Highest chlorophyll content: Ferbanat (4.0 L ha^{-1}), highest plant length: Ferbanat (2.0 L ha^{-1})	Highest yield: Ferbanat (3.0 L ha^{-1} for first year and 4.0 L ha^{-1} in second year) highest Av. fruit wt., fruit length in Nanonat (@ 4.0 L ha^{-1})	–	–	Ekinci et al. (2014)
	–	–	Pellets of jaggery and alginate containing neem cake + nanoNPK + PGPR	Mung bean (*Vigna radiata* variety KM2)	In vitro study	Seed germination and mean germination time enhanced	–	–	–	Celsia and Mala (2014)
Metal/metal oxide nanoparticles as Micronutrient nanofertilizers										
Zinc	Flower-like structures formed by gathering of closely packed nanometer scale rods	Nano-ZnO particles (@ 0, 400, 600, 800, and 1000 mg kg^{-1})	Seed mixing with powder nanoparticles	Tomato (*Lycopersicon esculentum* Mill)	In vitro study	Enhanced seed vigor index, reduced tomato seed deterioration during aging	–	–	–	Tamilkumar et al. (2016)
	Nano-ZnO with size <100 nm	30, 200, and 2250 mg Zn pot^{-1}	Soil application	Bean (*Phaseolus vulgaris var. contender*), Red cherry tomato (*Solanum lycopersicon var. cerasiforme*)	Greenhouse pot study using acidic and calcerous soils	Increased chlorophyll and carotenoids	–	–	–	García-gómez et al. (2017)

(continued)

Table 15.1 (continued)

Nanofertilizer evaluated	Size dimensions/ other characteristics	Test concentrations	Mode of application	Test vegetable crop	Study conditions	Traits evaluated or affected			Stress tolerance	References
						Vegetative	Yield attributing and yield	Quality attributing		
	Mean diameter of 30–40 nm	Nano-ZnO particles (@ 0, 100, 500 or 1000 mg kg DW^{-1})	10 mL of each concentration of nZn and nZnO particle suspension was added to seeds on filter paper in petri dish	Sweet potato (*Ipomoea batatas*)	Field study	–	Tuber length and diameter increased, tuber biomass, number and mass per tuber equivalent to control	Increased Zn concentration in tuber peel	–	Bradfield et al. (2017)
Iron	Average size of Fe_2O_3 NPs (30–40 nm)	Fe_2O_3 NPs @ 0, 100, 150, and 200 mg	Nano Fe_2O_3 NPs added in Hoagland's medium at three specific concentrations	Spinach (*Spinacea oleracea*)	Hydroponic study	Enhanced growth rate in nano-Fe treatment (root and shoot length, wet and dry biomass) in a dose and time-dependent manner		Enhanced (3.6 times) Fe content	–	Jeyasubramanian et al. (2016)
	Spherical shaped, size 52.4 ± 5.1 nm, Hydrodynamic size (143.8 ± 90 nm), zeta potential (−23.3 ± 1.2 mV)	Fe NPs @ 0, 0.05 and 2.0 mM	Irrigation with MS medium supplemented with Fe NPs	Chili (*Capsicum annuum*)	Pot experiment	0.05 mM L^{-1} Fe NPs: highest plant height, thinner leaves, more tightly packed mesophyll cells, thinner cell wall of mesophyll cells, higher chloroplast per cell, more grana lamellae per chloroplast	–	Significantly higher Fe content	–	Yuan et al. (2018)

(continued)

Table 15.1 (continued)

Nanofertilizer evaluated	Size dimensions/ other characteristics	Test concentrations	Mode of application	Test vegetable crop	Study conditions	Traits evaluated or affected			Stress toler-ance	References
						Vegetative	Yield attributing and yield	Quality attributing		
Copper	Average size range 40–60 nm	CuO NPs @ 0, 10, or 250 mg per plant	Foliar exposure of 3-week-old plants (4 or 5 leaves per plant with 2–4 cm^2 per leaf)	Cabbage (*B. oleracea* var. *capitate* L.) and *Lactuca sativa* L. cv. batavia blonde Doree)	Hydroponic study in RHIZOtest devices	Increased plant dry weight and stomatal conductance at 10 mg plant^{-1} CuO NPs concentration	–	Enhanced Cu concentration in leaves	–	Xiong et al. (2017)
Non-nutritional metal/metal or non-metal oxide nanoparticles as plant growth promoting agents										
Cerium	Triangular-, rectangular-, and other irregular-shaped NPs with average diameter ranging from 10 to 30 nm, hydrodynamic diameter (~600 nm), zeta potential (−11.9 mv)	CeO_2 NPs @ 0 and 10 mg L^{-1}	NPs incorporated in Hoagland's medium	Radish (*Raphanus sativus* L. Cherriette (F1))	Hydroponic study in 100 ml glass jars	Significantly higher dry shoot biomass in CeO_2 NPs treatment than control	–	Higher Ce presence in peridem of CeO_2 NP-treated roots	–	Zhang et al. (2015a)
Platinum	Pt NPs mean size (Δ50): 6 nm	Pt NPs aqueous suspension applied at 5 mg kg^{-1} soil	Pt NPs applied in soil before sowing and 45 days after seeding	Cucumber (*Cucumis sativus* L. cv. Masha)	Greenhouse study in 1 m^2 soil pitch (50 kg)	–	Yield capacity similar to control	Less Pt in roots	–	Astafurova et al. (2017)
Silver	Average size ~20 nm	40 g ha^{-1} colloidal nanosilver	Applied in irrigation water	Muskmelon (*Cucumis melo* L. cv. Ghasri)	Field study	–	AgNPs + Magnetic field treatment: highest fruit yield, fruit size	Significantly higher soluble sugars	–	Feizi et al. (2013)
Titanium	Spherical shape and average size of 19.5–20 nm	TiO_2 NPs @ 0, 2,4, and 6 ppm	Foliar spray	Coriander (*Coriandrum sativum* L.)	Field experiment	Significant increase in plant height, number of branches	Significant increase in yield	Significant increase in amino acids, total sugars, total phenols, total indols and pigments	–	Khater (2015)

(Song et al. 2017), and later incorporating the foliar or seedling root exposure of the nanomaterial component (Ghooshchi 2017) and treating the PGPRMs with nanomaterial under broth conditions for elicitation of extra polysaccharide production by microbes and then priming or coating of the vegetable seeds with nanomaterial primed PGPRMs (Palmqvist et al. 2015). Thus, effective stimulation for enhanced seed germination, seedling vigor, and growth can be obtained by this approach besides posing of less or negligible environmental impact due to containment of the nanocomponent onto seed surface or use of very low concentrations.

15.3.2 Nanopesticides for Pest and Pathogen Management in Vegetable Crops

Vegetable crops are vulnerable to pest and pathogen attack due to their more bulk/biomass, succulence due to high water content and invariably long and indistinctive vegetative growth phase leads to depreciation in yield and quality of the produce in field as well as during transport and storage (Nguyen et al. 2018). A variety of pests and pathogens including the plant stand reducers, photosynthetic rate decelerators, senescence accelerators, plant sap feeders/assimilators, and plant tissue devourers severely affect the yield, quality, and thus, the crop productivity in vegetables (Oerke 2006). Therefore, vegetable crop production claims a substantial amount of pesticides—which are used for both pre- and post-harvest application (Zhang 2018). However, the continuous use and low use efficiency of the applied pesticides have led to environmental, livestock, and human health complications (Rahman and Chima 2018). Leaching and runoff of the field-applied pesticides has led to contamination of the land and water resources (Kalia and Gosal 2011). Human lives have been claimed due to accidental/unintentional exposure of workers at pesticide production units, pesticide poisoning among the farm workers, and general public owing to consumption of pesticide-contaminated food grains, vegetables, and fruits with a death rate of twenty thousand per annum, particularly in developing countries (Devi et al. 2017). Therefore, there is an ardent need for the development of novel formulations of pesticide-active ingredients which can exhibit targeted release and impart protection from rampant losses.

Development of nanopesticides has commenced as nanoscaling of the active ingredient or adsorption of a.i. in or on nanovehicles will improve the solubility of poorly water-soluble organic compounds, can enhance their bioavailability (surfactant amended products to alter surface tension properties), will ensure for slow-/controlled release (encapsulated nanopesticides), as well as targeted delivery to the pest/pathogen of interest without drift losses to the environment (Ramadass and Thiagarajan 2017; Huang et al. 2018; Kah et al. 2018a, b). Nanopesticides have been developed and evaluated for insect/nematode/snail pests and bacterial/fungal and viral disease-causing pathogens in vegetable crops (Table 15.2).

Table 15.2 Nanomaterials evaluated for pesticide action or delivery of the pesticide-active ingredient for combating pests or pathogens of vegetable crops

Type of nanopesticide	Size dimensions/ other characteristics	Test vegetable crop	Pest/pathogen affected	Effective dosage	Mode of application/study conditions	Remarks	References
Silver NPs (PVP and *Trichoderma* cell-free derived)	Mean diameter (12.7–23 nm)	Potato (*Solanum tuberosum* L.)	*Alternaria solani* causative agent of early blight disease of potato	150 ppm	Foliar spray three times at 10 days interval/ Field study	Disease severity decreased	El-Batal et al. (2016)
Iron NPs (*Stenotrophomonas maltophilia* KBS 2.4 derived)	Mean diameter 70 nm	Okra (*Abelmoschus esculentus* L.)	*Meloidogyne incognita* causative agent of root knot disease	120 mg/ml	In vitro and in vivo pot experiment	Absence of juveniles 50 days after inoculation	Sharma et al. (2017)
Magnesium oxide NPs (Chemically synthesized)	Mean diameter 70 nm	–	*F. oxysporum* f. sp. *lycopersici* causative agent of Fusarium wilt of tomato	2%	In vitro study (poison food technique on agar media and broth supplementation)	Decreased growth on PDA and optical density in SDB	Parizi et al. (2014)
	Average diameter ranged from 20 to 200 nm	Tomato (*Solanum lycopersicum* cv. Momotaro)	*Ralstonia solanacearum* soil borne vascular pathogen of tomato	0.05 or 0.1% (in vitro expt.)	In vitro and in vivo pot experiment	Absence of *R. solanacearum* in vascular bundle and tylose accumulation in MgO NP-treated plants	Imada et al. (2016)
Silica NPs (loaded with fipronil insecticide)	Average size of 8, 25, and 44 nm	–	Worker termite (*C. acinaciformis*)	1 $mg\ mL^{-1}$ fipronil in Miglyol 812 oil	In vitro and in vivo experiment	First mortality in 4 h	Wibowo et al. (2014)

(continued)

Table 15.2 (continued)

Type of nanopesticide	Size dimensions/ other characteristics	Test vegetable crop	Pest/pathogen affected	Effective dosage	Mode of application/study conditions	Remarks	References
Poly (epsilon-Caprolactone) nanocapsules loaded with atrazine	average size distribution of 240.7 nm	Mustard (*Brassica juncea*) as model plant	Herbicide	atrazine at 1 mg mL^{-1}	Pot experiment	Decreased net photosynthesis, lowered PSII maximum quantum yield, high leaf lipid peroxidation	Oliveira et al. (2015)
Electrospun nylon-6/ chitosan nanofibers	–	–	*Pseudomonas cichorii* causative agent of bacterial leaf spot (bacterial midrib rot), *Dickeya dadantii* (*Erwinia chrysanthemi*) causing bacterial blight	–	In vitro study (agar disk diffusion method)	High potential antibacterial activity on bacterial protein synthesis	Abdel-Megeed et al. (2014)
Graphene oxide sheet loaded CuO NPs	Average size of 21.28 nm	Tomato (*Lycopersicon esculentum* cv. Shi Hong 9)	*Pseudomonas syringae* pv. *Tomato* causative agent of bacterial speck in tomato	4 and 8 mg mL^{-1}	In vitro and in vivo experiment	GO-Cu NPs: 16-times higher antibacterial activity than Kocide 3000 in vivo test: GO-Cu NPs (at 4 and 8 mg mL^{-1}) significantly reduced the severity of bacterial speck	Li et al. (2017)

15.3.3 Nano-Enabled Sensors: Quick and Early Detection of Pest and Pathogen Attacks and for Surveillance of Crop Health

The nano-enabled sensor devices are the point-of-care on-field sensing devices which can ensure real-time qualitative and quantitative sensing of a diverse kind of macromolecules/compounds of pest/pathogen origin for quick and accurate diagnosis of plant pest and disease agents (Khiyami et al. 2014; Lau et al. 2016). The functional platforms for fabrication of these devices are invariably portable, miniaturized, automated, and high-through put systems which can perform ultra-sensitive detection for presence of pest/pathogen or damage caused to the crop plant (Jianrong et al. 2004).

The major components of a sensor device include the receptor, transducer, and digital display system for reception of the detectable compound/ligand, conversion of reception to measurable entity, and finally its display in specific units, respectively (Rai and Ingle 2012). Sensors which utilize bio-receptor molecules such as proteins, enzymes, nucleic acids, and other macromolecules are termed as ‘bio-sensor’ systems. Incorporation of a nanomaterial on a receptor or transducer or receptor–transducer interface can modify it to generate a ‘nanobiosensor,’ having enhanced sensitivity, selectivity, speed, and ability of multiplexed analysis of complex samples (Rai and Ingle 2012; Rai et al. 2012; Khiyami et al. 2014; Omanović and Maksimović 2016). The relevance of these rapid sensor systems is utmost for vegetable cultivation as the losses incurred on attack by pest/pathogen are high due to greater yield penalties (Lau et al. 2016). The nanomaterials utilized for the fabrication of these sensor systems may vary in their chemical composition. Non-metals such as silica nanoparticles (Yao et al. 2009) have been used for their fluorescent properties. Likewise, metals (Popescu et al. 2015) such as, gold (Verma et al. 2015) and silver (Donoso and Valenzuela 2018) nanoparticles find sensor applications due to higher electro-activity, surface plasmon resonance and electric conductivity (Fang and Ramasamy 2015). Meanwhile, the semi-conductor nanocrystals or quantum dots (Safarpour et al. 2012) have been used to fabricate fluorescence based sensors and several others. The nucleic acid-based POCs have also been developed for plant pathogen detection with the advent of isothermal DNA amplification techniques coupled with lateral flow strips and portable fluorometers (Wang et al. 2017; Donoso and Valenzuela 2018).

Nanosensors exhibit another exciting feature that is the possibilities to integrate all the individual components through satellite/internet or wireless systems (Akyildiz and Jornet 2010; Kakade et al. 2016). Therefore, there is a scope of development of low-cost may be smart-phone based platforms that can be utilized for surveillance monitoring of pest attack or disease severity in the crop under field conditions (Omanović and Maksimović 2016; Rateni et al. 2017; Donoso and Valenzuela 2018). The Internet of things (IoT) technology platforms can further integrate the farm operations, crop surveillance and decision support systems, and end-user, i.e., farmer interactive services online/off-line for a better control/monitoring of the pest/pathogen attacks (Shi et al. 2015).

15.4 Nano-Based Products: How to and What's Ahead?

Embracing nanotechnology as one among the key enabling technologies in agriculture sector offers a bright opportunity for realization of the concept of enhanced produce quality, food safety, and security besides capitalization of associated ecological and economic benefits (Prasad et al. 2017; Raliya et al. 2017). Indian government iconized the possible benefits of nanotechnology interventions in agriculture and industry, and the funds were allocated in the Ninth Five-Year Plan. This was followed by formation of a core expert group, Nanomaterials Science ad Devices by DST which flourished to Nano Science Technology Mission, now guided by two advisory groups, viz., Nano Science Advisory Group (NSAG) and the Nano Applications and Technology Advisory Group (NATAG) (Kumar 2014).

15.4.1 Nano-Based Patents and Commercialized Products

There is an increasing awareness among the researchers for their intellectual property (Jain et al. 2011). The Government of India has even established a specific institute for training, management, research, and education in the field of intellectual property rights, i.e., National Institute of Intellectual Property Management, Nagpur, Maharashtra. The arising awareness has led to a swarm of number of patent applications which are being filed claiming the novelty and industrial applications of processes and products. The World Intellectual Property Organization, Geneva, has published a report on World Intellectual Property Indicators 2017 which indicated China as the front-runner country (Fig. 15.2) overtaking the world's innovation leaders such as Japan, Germany, and South Korea (Santacreu and Zhu 2018) regarding filing of applications for obtaining patents, trademarks, industrial design, and utility models across globe (http://www.wipo.int/edocs/pubdocs/en/wipo_pub_941_2017.pdf). Likewise, filing of the patent applications in India is rising, fetching us nineteenth rank all over the world. However, unfortunately for Asian countries such as China, India, and others, the sub-set of filed applications which are granted patent are not equivalent to the application filing standards.

The scenario for filing of the patent applications for nanotechnology-enabled/-inspired process and products is similar (Singh 2017). Ironically, it is not an appropriate indicator of the innovation-driven technology in agriculture and industry. The nanotechnology-related patents involve filing of patent applications for both process and product categories (Jain et al. 2011). The nanotechnology innovations are more required to be guarded intellectually through filing patents in country and overseas. Three countries, viz., USA, Germany, and Australia, are filing patent applications in India to safeguard the process or product developed and patented in their own territory (Bhattacharya and Shilpa 2011).

Asian countries have an agri-based economy such as India; therefore, strenuous efforts are desired for nano-interventions in agriculture, and nano-enabled research

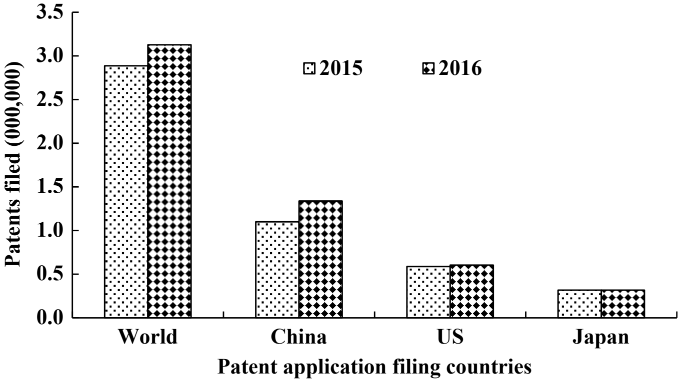

Fig. 15.2 Patent applications filed in world and from predominant countries for the years 2015 and 2016

has to be fathomed for effective and prudent agri-technological solutions. The nanopatent swarming is not translated to commercially viable nanoproducts of agri-importance (Parisi et al. 2014). There are few examples of commercially available nanofertilizer or -pesticide formulation (Dimkpa and Bindraban 2018) though the authenticity for the presence of nanoscale component in these preparations is still debatable. This is practically due to the requirement of heavy investments and high economic cost for the nanoscaling of the fertilizer nutrient or the pesticide a.i. which cannot be off-set by even mass scaling up of the manufacturing technologies as has been practiced for nano-inspired products in medical and pharma sector (Parisi et al. 2014). Another hitch for realization of commercial nanofertilizer or nanopesticide is the uniformity of the particle size at nanoscale, its percentile content in the formulation, and reproducible standard technique(s) for identification. Moreover, there are no separate specific regulations addressing nanoparticulate formulations of the fertilizers and pesticides in European Union, and there is a similar scenario for USA and Canada (Parisi et al. 2014). Regulatory bodies in Asia are at their inception, and likewise quarantine toolbox and measures have to be designed for nano-enabled/-inspired products for agricultural use.

15.5 Safety Concerns

Engineered nanomaterials (ENMs) exhibit unique behavior digressing from bulk counterparts (Jeevanandam et al. 2018). Therefore, there are enormous possibilities of alternative interactions in myriad of ways with the components of the ecological niche(s) on intentional application of nanomaterials (Buzea et al. 2007; Kah and Hofmann 2014; Kah et al. 2018a, b). Thus, ENMs are anticipated to possess variable solubility, extent/amount of bioavailability, transformation kinetics, and transportation mechanisms in comparison to their elemental bulk forms complicating the possibility of prediction of their behavior in open and dynamic systems (Ke and Lamm 2011; Salonen et al. 2016; Eymard-Vernain et al. 2018). Further, tagging engineered nanomaterials as ‘green and clean’ to fulfill their role in sustainable vegetable production, protection and storage demands comprehensive assessment of their ecological and human health perspectives through use of a battery of tests employed for analyzing all the critical phases of nanomaterial production, application, and end-of-life stages (Pallas et al. 2018). Thus, forfeiting the ecological safety of ENMs is challenging as it will involve mapping the impact of both intentional and unintentional application for the whole life cycle stages of nano-based products (Pallas et al. 2018).

Application of nanoagri-chemicals for vegetable crop production and protection can be realized if the nanoproducts could be economically affordable besides eco-safe as these products have to address the problems and issues of the resource-poor and marginal growers (Kah 2015). In general, vegetables are voracious nutrient mining crops and have their specific requirements; thus, crop specific nanofertilizer application strategies have to be customized. There is a dilemma for wide-spread embracement of the products of nanotechnology for vegetable cultivation among the growers which need to be shunned through series of tests of imperative risk assessment toolbox. Moreover, a variety of socio-psychological factors are impairing the societal acceptance and stigmatization of the nanotechnology products in agriculture due to analogies drawn with genetically modified food in spite of a positivity for biomedical and environmental applications of nanotechnology (Parisi et al. 2014).

15.6 Conclusions

Vegetables are indispensable components of a healthy diet as these are rich sources of minerals, phytochemicals, bio-active compounds, and other compounds of nutraceutical importance. However, the production costs are escalating due to high agri-input requirement for cultivation of vegetables, which has culminated to emergence of problems such as incidences of heavy pesticide residue load, lack of organized infrastructural and marketing framework to address seasonal shortage and glut issues, and effective and faster transportation and storage facilities that are required to be addressed. Therefore, new interventions under the nano-umbrella can possibly chalk-out the paradigm for long-felt agri-technological desire of sustainable vegetable production.

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Chapter 16
Nanocellulose from Agro-Residues and Forest Biomass for Pulp and Paper Product

N. Vigneshwaran, A. K. Bharimalla, A. Arputharaj and P. G. Patil

Abstract Nanocellulose, a nanoform of cellulosic material, is a newer material showing interesting properties and has potential for diversified applications. Nanocellulose, having any one of the dimensions in the size range between 1 and 100 nm, is extracted from cellulosic biomass derived from plants, animals, or microbial origin. Cotton and other natural lignocellulosic fibers, agro-residues, forest biomass, and bacterial cellulose are important raw materials to produce nanocellulose. In the top-down approach of synthesis, the macroscale cellulosic particles are converted into nanocellulose by mechanical, chemical, or biological ways or their combinations. The extracted nanocellulose can be spherical or whisker-shaped nanocellulose (NCC) and nanofibrillated cellulose (NFC); but many other nomenclatures are also being used like cellulose nanofibres (CNF), nanocellulosic fibers (NCF), cellulose nanocrystals (CNC) and microfibrillated cellulose (MFC). Nanocellulose exhibits very large surface area to volume ratio, high level of crystallinity, liquid crystalline behavior, thixotropic behavior, and enhanced mechanical properties. Major areas of applications include furnish and coating additive in paper, filler in packaging and composites, non-calorific additives in food materials, thickening agents in paints and adhesives and as fillers and carriers in pharma products. Other areas of applications could be reached after surface chemical modification of nanocellulose. Pulp and paper industries are the first one where the nanocellulose is being used commercially for improving the strength, printability, and barrier properties of paper. Nanocellulose also helps to reduce the weight of the paper without compromising its strength and other quality parameters. This chapter covers the various aspects of nanocellulose production, characterization, and application in pulp and paper product.

Keywords Nanocellulose · Agro-residues · Forest biomass · Lignocellulosic fibers · Paper · Packaging

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16.1 Introduction

Lignocellulosic biomass, like agro-residues and forest biomass, forms the largest source of raw materials to produce pulp and paper, bioethanol, syngas, hydrogen gas, construction materials, specialty chemicals and bio-based composites. They are going to be a major competitor for the petroleum-based products. The main components of any lignocellulosic biomass include cellulose, hemicellulose, lignin, and minerals. Lignin provides stiffness, water impermeability, and microbial resistance to the material. Hemicellulose, a heteropolymer of pentoses and hexoses, attaches to cellulose through hydrogen bonding and Van der Waal's forces. Cellulose imparts strength and water insolubility of the biomass. Cellulose is a linear polysaccharide with the molecular formula of $(C_6H_{10}O_5)_n$, containing $\beta(1 \rightarrow 4)$ linked D-glucose units. Cellulose is an important structural entity of primary cell wall of plants, cotton fibers, and algae. They are also present in fungi, tunicates, and bacteria.

Among the various natural sources of cellulose (Fig. 16.1), cotton and bacterial sources yield the purest forms of cellulose. In other biomasses, cellulose is present in combination with lignin and hemicellulose. The orderly region of cellulose due to hydrogen bonds forms the crystalline region and other parts constitute the amorphous region. The crystalline regions are very stable structures against hydrolysis, and they contribute to the stiffness and strength of cellulosic materials. The amorphous region contributes to the softness and flexibility of cellulosic materials. The presence of crystalline region in cotton fibers is the highest, and hence they exhibit better mechanical properties in comparison with other cellulosic fibers. Also, the degree of polymerization (number of glucose polymers in the linear chain of cellulose molecule) is very high (more than 10,000) in case of cotton compared to other agro-residues and forest biomass (less than 1000). These materials are being used for extracting the nanocellulose which is being discussed below.

Fig. 16.1 Various sources of cellulose

16.2 Nanocellulose

Nanocellulose is a natural nanomaterial extracted from the cellulosic biomass, having the size of any one dimension <100 nm. The nanodimension imparts very high specific strength, improved stiffness, high surface area, and thixotropic property to nanocellulose. In addition, in their basic structure, nanocellulose consists of a lot of –OH groups that could be available for surface modification for potential applications in pharmaceuticals, biomedical products, nanocomposites textiles, and so on (Phanthong et al. 2018). The use of cellulosic residues and other waste materials derived out of agricultural and industrial processes is increasing due to their widespread availability and renewable character (García et al. 2016). The schematic structural arrangements of cellulosic nanofibrils and nanocrystals inside the wood biomass and agro-residues are given in Fig. 16.2. The various cellulosic sources like agro-residues and forest biomass and their extraction methods for nanocellulose tried recently are summarized in Table 16.1.

Most of the nanocellulose production protocols involve the use of very strong chemicals like concentrated sulfuric acid or TEMPO oxidation and mechanical processes like high-pressure homogenization or friction grinding. They are either producing lot of effluent or requiring huge amount of energy, thereby reducing their widespread usage in various applications. The various types of classifications of

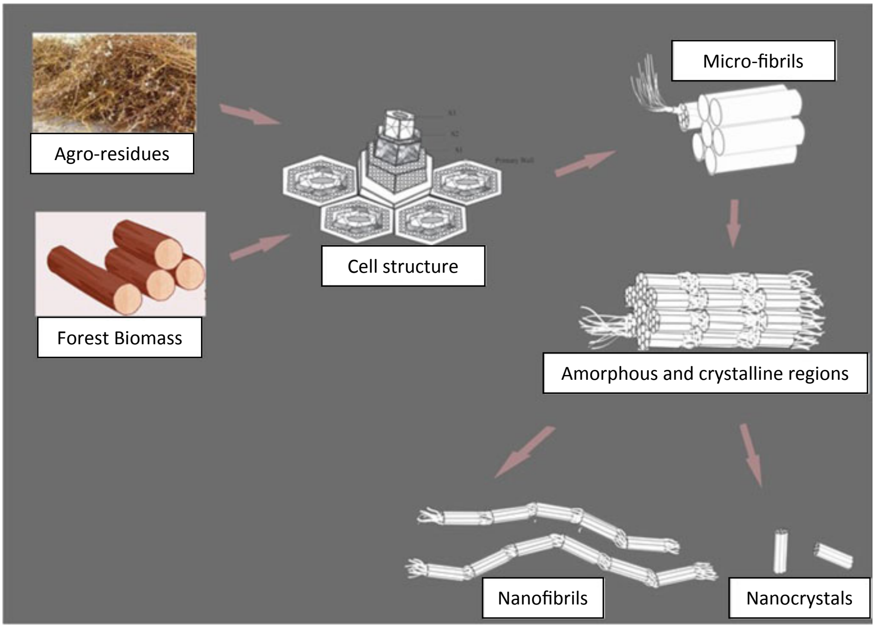

Fig. 16.2 Schematic of the structural features of cellulosic nanofibrils and nanocrystals being extracted from the agro-residues or forest biomass

Table 16.1 Nanocellulose extraction from various cellulosic biomasses

S. No.	Agro-residues/ Forest biomass	Product	Methods	Dimension range	References
1	Sugarcane bagasse fibers and pith	Nanocellulose	High-pressure homogenization	10–20 nm diameter	Li et al. (2012)
		CNCs	Acid hydrolysis	69–117 nm length 6–7 nm diameter	Camargo et al. (2016), Oliveira et al. (2016), Wulandari et al. (2016)
2	Grape pomace	CNCs	Acid hydrolysis and ultrasound treatment	Lengths 307–323 nm and diameters 7–8 nm	Coelho et al. (2018)
3	Cotton and cotton stalk bleached pulps	NCC, CNF	Acid hydrolysis, TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl) oxy radical]-mediated oxidation process	3–15 nm width and 10–100 nm length	Morais et al. (2013), Shamskar et al. (2016), Soni and Mahmoud (2015), Thambiraj and Shankaran (2017), Zhou et al. (2017)
		Ribbon-like CNC	cellulase enzymolysis	Length 250–900 nm and width 30–45 nm	Chen et al. (2019)
4	Corn stalks	NFC	(2,2,6,6-Tetramethylpiperidin-1-yl) oxyl (TEMPO)-mediated oxidation followed by high speed blending	10–25 nm width	Boufi and Chaker (2016), Cheng et al. (2018)
5	Seed fibers of Ushar (*Calotropis procera*)	CNC CNF	Acid hydrolysis TEMPO-mediated oxidation	Diameter of 14–24 nm and length of 140–260 nm Long fibrous structure with the diameter of 10–20 nm	Oun and Rhim (2016)
6	Brazilian satintail (*Imperata brasiliensis*) plant	CNs	Acid hydrolysis	Diameter from 10 to 60 nm and length in between 150 and 250 nm	Benini et al. (2018)

(continued)

Table 16.1 (continued)

S. No.	Agro-residues/ Forest biomass	Product	Methods	Dimension range	References
7	Softwood biomass	CNCs NC fibrils	AVAP® biorefinery technology	Width: 4.5 ± 1.5 Length: 222 ± 139 Width: 29 ± 18 nm Length:1627 ± 1252 nm	Kyle et al. (2018)
8	Eucalyptus pulp	Nanocellulose	High-pressure homogenization	20–100 nm diameter	Wang et al. (2017)
9	Saw dust	CNCs	chemically engineered hydrothermal process	~18–35 nm diameter range, lengths in the range of ~101–107 nm	Kalita et al. (2015)
10	Walnut shells	CNCs	Acid hydrolysis combined with sonication and homogenization	Diameter of CNCs was 130 nm	Hemmati et al. (2018)
11	Tomato peels	CNCs	Acid hydrolysis	average width 42 nm	Jiang and Hsieh (2015)
12	Pinecone of Jack pine (*Pinus banksiana*)	NCF	Chemical and mechanical treatment	Diameter range between 5 and 25 nm	Rambabu et al. (2016)

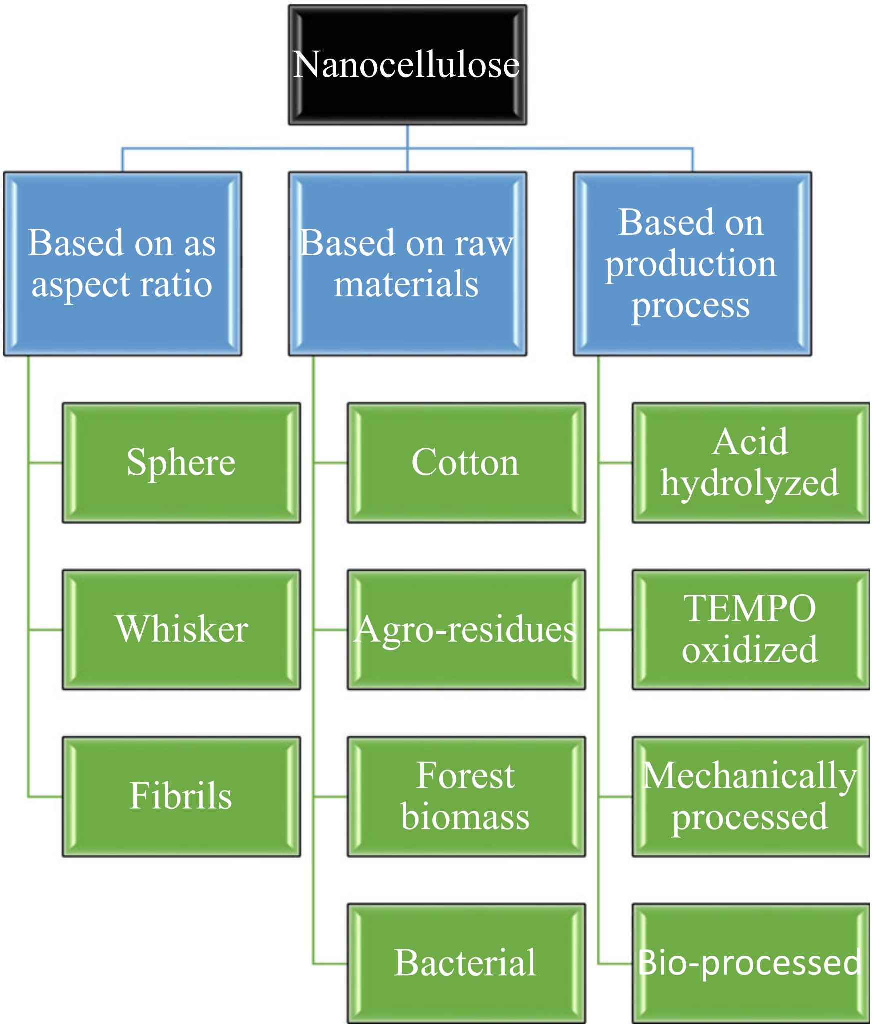

Fig. 16.3 Classification of nanocellulose based on different parameters

nanocellulose are given in the Fig. 16.3. They are classified based on their morphology, raw materials, or by the production protocol used. The type of required nanocellulose needs to be finalized based on the end-use applications.

Our research group at ICAR-Central Institute for Research on Cotton Technology, Mumbai is working on the production of nanocellulose from cotton linters and other agro-residues like banana fibers and sugarcane bagasse. Also, a pilot plant facility is installed with a capacity to produce 10 kg of nanocellulose per day for use in industrial trials for product development. The methodology being used for production of nanocellulose preparation is a patented chemo-bio-mechanical process (Bharimalla et al. 2015, 2017; Vigneshwaran and Satyamurthy 2016; Vigneshwaran et al. 2015).

16.3 Characterization of Nanocellulose

Though basically made from the cellulosic substrate, the size, morphology, shape, surface charge and flow behavior vary greatly according to the source of raw material and the method of production. By considering the different applications of commercial interest, it is very much essential to carry out comprehensive evaluation of structure and other properties of nanocellulose. Normally, some of the characterization methods are used to analyze the sizes, shapes, and morphology of nanocellulose and others are used to obtain in-depth structural information. Figure 16.4 shows the overall methodologies being adopted for characterization of nanocellulose.

To understand the size dependent properties, following parameters need to be analyzed:

- Size, size distribution, shape, and aspect ratio
- Degree of aggregation and agglomeration
- Surface chemistry (zeta potential and surface functional groups)
- Crystal size and structure
- Optical properties
- Mechanical properties
- Rheological properties, and
- Electrical properties.

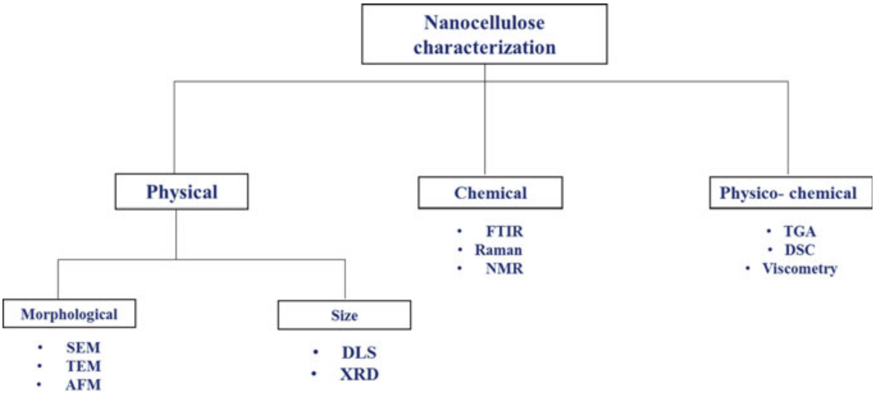

Fig. 16.4 Different analytical tools used for the NC characterization

16.3.1 FTIR Analysis

In practice, infrared radiation (400–4500 cm^{-1}) of successively increasing wavelength is passed through the sample and the percentage of transmittance is measured using an infrared spectrophotometer. Attenuated total reflection (ATR) is one of the accessories of FTIR to analyze the surface properties of solid film samples or thin film samples rather than analyzing their bulk properties. The characteristic peaks for the cellulose molecule (Oh et al. 2005; Satyamurthy and Vigneshwaran 2013) are hydrogen bond stretching at the wavenumber of 3299 cm^{-1}, OH bending of adsorbed water at 1644 cm^{-1}, the stretching of CH at 2921 cm^{-1}, the HCH and OCH in-plane bending vibrations located in 1430 cm^{-1}, CH deformation vibration at 1373 cm^{-1}, the COC, CCO, and CCH deformation modes and stretching vibrations in which the motions of the C-5 and C-6 atoms are at 850 cm^{-1}, and C–OH out-of-plane bending mode is located at 670 cm^{-1}. Mostly, cellulose will not change its chemical functionality after the conversion into nanocellulose because the changes are happening in its physical structure. However, some new functional groups may be added into the cellulose molecules which depend upon the nature of synthesis. For example, after the oxidation of cellulose, intensity of band at 1700–1750 cm^{-1} increases indicating an increase in quantum of carbonyl and carboxyl groups.

FTIR can also be used for comparative evaluation of cellulose crystallinity by measuring the relative height of two different peaks. A crystallinity index (CI) is the ratio of a particular peak related to crystallinity with respect to a peak that is not representing the crystallinity within the spectrum. The relative crystallinity index for the cellulose is determined by measuring the ratio of absorbance at 1428 cm^{-1} and at 900 cm^{-1}. This ratio indicates the relative amount of crystalline and amorphous portions in a cellulosic material.

16.3.2 Raman Analysis

Raman spectroscopy, a kind of vibrational spectroscopy, is used to find information about molecular vibrations and crystal structures with the help of a laser light source. On irradiation of the sample, an infinitesimal amount of Raman scattered light is formed that is detected and analyzed as a Raman spectrum. The characteristic fingerprinting pattern of a Raman spectrum of polymer makes it possible to detect polymorphs, crystallinity, orientation, and stress. Analysis of nanocellulose suspensions by Raman spectroscopy is very useful technique in nanocellulose characterization since the analysis can be carried out native hydrated state without special requirements. Numerous information can be obtained from the Raman spectra like estimation of crystallinity (in suspensions and freeze-dried states), measurement of accessibility, detection and quantitation of cellulose II polymorph in NCs, and effect of drying on the structure of NCs. Raman spectra of the NCs contain bands that are associated with chemical functionalities usually present on the surfaces. Sulfate esters present on the surfaces of NC can be quantified by Raman spectroscopy. The index of crystallinity can be calculated from the ratio of the peak's height at 380 and 1096 cm^{-1}.

16.3.3 Dynamic Light Scattering (DLS) Analysis

Dynamic light scattering (DLS) is a valuable technique used for size analysis of nanocellulose and other nanomaterials. The analysis of scattered light helps to determine particle size, molecular weight, and zeta potential. Nanocellulose in dispersion are in constant Brownian motion due to the thermal energy. The speed of the Brownian motion of the particles is measured from their scattered light by a technique known as photon correlation spectroscopy or DLS. The observed intensity of scattering dependents on the particle size and reduces with the reduction in particle's cross-sectional area. Sample preparation either by filtration or centrifugation is critical to remove dust and artefacts from the suspension. The hydrodynamic diameter is obtained based on dynamic light scattering and autocorrelation principle. The mean diameter of particles is calculated from Brownian motion via Stokes–Einstein equation (Edward 1970).

$$d_{\mathrm{H}} = \frac{kT}{3\pi\eta D}$$

where
d_{H} = hydrodynamic diameter (m)
k = Boltzmann constant (J/K = kg m^2/s^2 K)
T = temperature (K)
η = solvent viscosity (kg/m s)
D = diffusion coefficient (m^2/s).

The stability of colloidal material is analyzed through their zeta potential. Zeta potential is an indirect measurement of the surface charge and it can be obtained by evaluating potential difference between the outer Helmholtz plane and surface of shear. Low-angle zeta potential analysis by electrophoretic light scattering can be used for the analysis of surface charge. The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. If all the particles have higher zeta potential, they will repel each other which will maintain dispersion stability. If particles have lower zeta potential, then there is no force to prevent the particles coming together and it induces the instability in the dispersion.

16.3.4 Wide-Angle X-Ray Diffraction (XRD)

XRD is one of the most essential tools used in characterization of the crystal structures. Evaluation of crystal structure is very much important even for nanoscale materials. Though a material's properties may be affected by structures on the nanometer scale, its crystal structures are determined by arrangement of atoms. The principle of XRD is based on the well-known Bragg's law ($\lambda = 2d\sin\theta$). Cellulose exists in several crystalline allomorphs: cellulose I_α and I_β (native forms), cellulose II (prepared regeneration or sodium hydroxide treatment), and cellulose III (prepared by liquid NH_3 treatment). Evaluation of these allomorphs of cellulose can be done by determining positions of the important diffraction peaks in XRD of cellulose. The crystalline domain diameter (D) or grain size is obtained from XRD peaks using the Scherrer's equation (Monshi et al. 2012).

$$D = K * \lambda/\beta * \cos\theta$$

where λ is the wavelength of the incident X-ray beam; θ is the Bragg's diffraction angle; β is the width of the X-ray pattern line at half peak—height in radian and the dimensionless shape factor (K) has a typical value of 0.89 but varies with the actual shape of the crystalline. It is expected to get broader peaks in XRD once the material is converted into bulk form to nanoform due to reduction in the grain size.

The determination of XRD crystallinity implies use of a two-phase model, i.e., the sample is composed of crystals and amorphous and no regions of semi-crystalline organization. The diffraction profile is divided in two parts, i.e., peaks are related to diffraction of crystallites and broad scattering alone is related to the amorphous scattering.

Total intensity = $I_a + I_b$

I_a = Intensity of crystalline phase (020 plane)

I_b = Intensity of amorphous crystalline phase

$$\text{Degree of crystallinity} = \frac{I_a}{I_a + I_b}$$

16.3.5 Small-Angle X-Ray Scattering

Small-angle X-ray scattering (SAXS) helps in the evaluation of sizes of small particles ranges from several to 100 nm by analyzing the scattered intensity of the X-rays in an angular range from 0.1° to 3°. In contrast to XRD, SAXS can be applied not only to the crystalline materials but also for amorphous materials. The SAXS intensity mainly depends on electron density and the form factor [$F(q)$]: $q = 4\pi\sin\theta/\lambda$, where θ is scattering angle and λ is wavelength of X-ray of the particle and the structure factor [$S(q)$]. The basic application of SAXS is the evaluation of particle size, shape, orientation, and size distribution in dilute dispersions, where the particle–particle correlation factor, $S(q)$, is negligible.

16.3.6 Electron Microscopy (TEM, SEM)

Electron microscopy uses electrons having shorter wavelengths thereby allowing the observation of matter down to atomic resolution. Two categories of electron microscopes are popularly used. In the scanning electron microscope (SEM), the electron beam is scanned over surface of an object to analyze the scattered electrons. The electron beam is generally scanned in a raster scan and the beam's position is merged with detected signal to produce an image. SEM can achieve resolution down to 1 nm. Specimens can be observed in vacuum or in ambient condition as in the case of ESEM. Transmission electron microscopy techniques (TEM) provide imaging, diffraction, and spectroscopic information of the specimen with an atomic and sub-nanometer spatial resolution. The sample preparation for TEM is tedious and time-consuming due to its requirement to be ultra-thin for electron transmittance. High-resolution TEM imaging in combination with the nanodiffraction and atomic resolution is very important to the fundamental studies of importance to nanotechnology. For TEM characterization, the nanoparticles dispersion is deposited onto the surface of grids and dried. For organic materials like nanocellulose, after dispersion, they needed to be fixed using a negative staining material (uranyl acetate).

16.3.7 Atomic Force Microscopy

AFM is ideally suited for characterizing many types of nanomaterials and it offers the capability of 3D visualization and semi-quantitative information on most of the physical properties like size, morphology, surface texture, roughness, and elasticity. The major advantage of AFM in comparison with other techniques is its ability to work in ambient air, vacuum, and under liquid environment. With an SEM/TEM, the images measured are only in two dimensions while the images from an AFM represent data in three dimensions, so that it is possible to measure the height or depth of the nanosurfaces. With an AFM, the mechanical characterization of nanomaterials is possible as the probe is in very close interaction with the sample while that is not possible in case of SEM or TEM. With neatly prepared samples (clean, with no excessively large surface features), resolution in the x–y plane ranges from 0.1 to 1.0 nm and in the z-direction is 0.01 nm. AFM requires neither a vacuum environment nor any tedious sample preparation techniques. With these advantages, AFM has significantly impacted various fields like materials science, chemistry, biology, physics, and semiconductors. The radius of AFM tip is around

5–50 nm and hence, it can probe extremely small interaction area with high sensitivity to small forces. These probes are suspended on a very soft spring made of silicon or silicon nitride beams thus allowing forces in pico-Newton range to be measured. This corresponds to the magnitude of forces that are required to break a single hydrogen bond. In the imaging mode, the cantilever having probe is scanned over the surface while in "force spectroscopy," the cantilever is moved directly toward the sample until contact and retracted again, while their interaction is measured.

16.3.8 Physico-Chemical Methods

Thermo analytical methods like differential thermal analysis (DTA) and thermogravimetric analysis (TGA) provide information about various physical and chemical changes, accompanied by heat of enthalpy. In thermal analysis nanocellulose, we can understand the sorption desorption, oxidation, and thermal decomposition properties. Differential scanning calorimetry (DSC) of typical cellulose shows an endotherm ranging from 360 to 385 °C with a peak at 372 °C corresponding to depolymerization of cellulose with the formation of flammable gases like pyro-glucosan and levo-glucosan. At this temperature, pyrolytic degradation of cellulose takes place with a rapid cleavage of the glucosidic bond. The shifting of this endothermic peak along with increase in intensity for nanocellulose was observed due to increase in amount of crystalline region (Satyamurthy and Vigneshwaran 2013).

16.4 Application of Nanocellulose for Pulp and Paper Products

The major types of nanocellulose applications in paper industries are discussed below and depicted in Fig. 16.5.

16.4.1 Coating Additive

In paper coatings, the quality of final printing is dictated by coating uniformity, pore structure, and chemical nature of the surface. Nanocellulose, due to its size range and rheological behavior, could be a potential substitute for the natural and synthetic co-binders, including modified starch, carboxymethyl cellulose (CMC), and polyacrylic thickeners. The nanocellulose additives are reported to operate as water-binding gel-forming components rather than the flocculating thickening

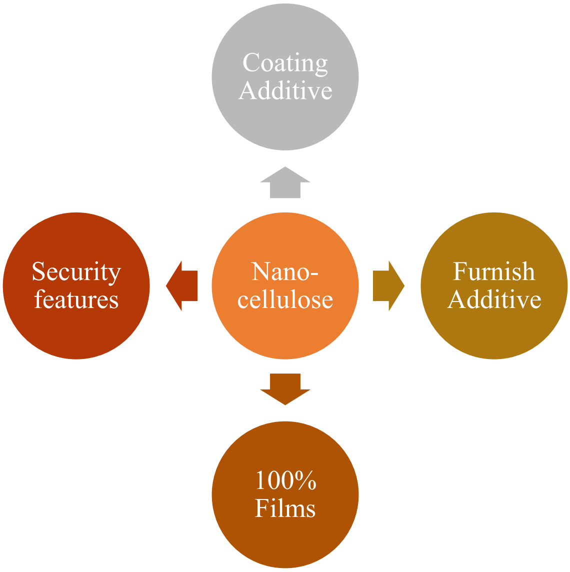

Fig. 16.5 Areas of applications of nanocellulose in paper industry

action of CMC. Immobilization of color in presence of nanocellulose is identified as a point of gel–water entrapment rather than the traditional stick–slip particle–particle interlocking mechanism predominating in traditional flocculant thickener formulations (Dimic-Misic et al. 2013). In another study, the impact of nanocellulose on rheological behavior of paper coatings were comparatively evaluated and showed that nanocellulose prepared by sulfuric acid hydrolysis and TEMPO oxidation exhibited very large dimensions, limited negative surface charge, and hence poor stability in their aqueous suspensions, while the FCN aqueous suspension displayed the highest viscoelastic modulus due to the formation of highly entangled network. And, sulfuric acid hydrolyzed nanocellulose exhibited strong interactions with pigments and immobilized water molecules, in comparison with other two types of nanocellulose evaluated (Liu et al. 2017).

Different processes like extrusion, curtain, size press, bar, and dip coatings are routinely used for coating of various additives on the surface of paper. The creation of bio-based nanocomposite coatings on the paper provides the opportunity to maintain a combination of favorable barrier properties toward low oxygen and water vapor permeability (Rastogi and Samyn 2015). Medical application of the NFC coated paper was also reported (Liu et al. 2015) wherein, the paper coated with triclosan-loaded NFC demonstrated excellent antibacterial activity against *E. coli* in addition to improving their tensile index (18.0%) and tear index (26.45).

16.4.2 Furnish Additive

NFC is always used as a furnish additive to improve the mechanical properties of the paper. In an earlier report, the eucalyptus pulp was reinforced with NFC and the best mechanical and physical results were reported with 6–9 wt% of NFC. But, the use of NFC resulted in drainage difficulties. At 3 wt% of NFC, it was possible to reduce the intensity of beating without affecting the final quality of paper (González et al. 2012). Another study reported that addition of 9 wt% of CNF (produced by TEMPO oxidation followed by mechanical homogenization) increased the tensile index of paper by around 95%, equivalent to that produced by the PFI refining at 1600 revolutions. This did not affect the paper machine runnability (Vallejos et al. 2016). It was also demonstrated to decrease the absorption of water to about 23.1% by the addition of acetylated NFC to non-acetylated pulp in addition to improving the mechanical properties like tensile and burse strength (Mashkour et al. 2015). In addition to these studies, there are other reports on the potential use of nanocellulose for reinforcing for paper (Kajanto and Kosonen 2012; Osong et al. 2014; Sun et al. 2015).

16.4.3 100% Films

The films made up of 100% nanocellulose, also called as self-standing films, are being used as a substrate for flexible electronics and sensors (Hu et al. 2013). The ample opportunities for surface modification of cellulosic molecules in addition to their strength and biodegradability make them an ideal material for the substrates of nanosensors. The periodate oxidation of nanocellulose results in films with an elastic modulus of 11 GPa followed by ozone treatment that induces conversion of aldehyde into carboxyl functionalities. The crystalline cellulose "Janus" film is suggested as an interfacial component in biomaterial engineering, separation technology, or in layered composite materials for the tunable affinity between the layers (Nypelö et al. 2018). Another study reported that the periodate-based nanocellulose films showed very high tensile strength (130–163 MPa) and modulus (19–22 GPa) and also superior oxygen barrier properties (as low as 0.12 cm^3 μm/(m^2 d kPa) at 50% relative humidity) (Sirviö et al. 2014). Another research group demonstrated to control the oxygen permeability of highly hydrophilic nanocellulosic film at elevated humid conditions with a simple surface modification strategy by the APTES-chemistry. Such modification resulted in a very thin layer with the nanometer-range thickness and hence proved very efficient (Peresin et al. 2017).

16.4.4 Security Features

Counterfeiting of important certificates, land documents, and currency notes is a serious issue in various countries. This results in increased focus by various researchers to develop novel anti-counterfeiting materials using nanotechnology. The use of a nanocellulose latex blend as an ink for security printing was reported wherein the inks are recognized as being special in its diffuse reflection, if polarizers are inserted between the light source and the paper and, also, between paper and the observer (Chindawong and Johannsmann 2014). Ink made using nanocellulose appears peculiar as it scrambles the polarization from background without being a strong scatterer itself. This application requires a dark background; applied to black paper, the contrast strongly depends on whether the printed area is viewed with polarizers being parallel/crossed.

Rapidly responsive and flexible photonic papers are manufactured by co-assembly of nanocellulose and waterborne polyurethane latex for fully utilizing the advantage of the chiral nematic structure of nanocellulose and the flexibility of the latex polymer. The resulting composite papers exhibit not only tunable iridescent colors, but also instant optical responses to water, ascribed to the easy chain movement of the elastomeric latex that does not restrict the fast water absorption-induced swelling of nanocellulose (Wan et al. 2018). Apart from security applications, this methodology will be of immense use in sensors and photonic circuits. Another research reported a family of new amino resin–cellulose nanocrystal composites. Owing to the chiral nematic order of the nanocellulose embedded in amino resin polymer, the materials appear highly iridescent and their color could be manipulated by the addition of salts. Also, the colored chiral nematic patterns could be permanently recorded in a composite film, suggesting their potential application in security features and sensors (Giese et al. 2013).

16.5 Conclusion

Lignocellulosic biomass is the most abundant and renewable polymer on Earth and its conversion would produce the novel material, nanocellulose. This adds value to the forest biomass and agricultural residues. To meet the ever-increasing demand for high-quality paper without any additional cost, nanocellulose offers a hope for such production. Apart from the use of nanocellulose in pulp and paper industries, it can be used as substrate for immobilization of chemical, microbial and enzyme catalysts. Also, the synthesis of synthetic rubbers, bioplastics, and pharmaceutical molecules from nanocellulose would be a quantum leap in nanocellulose industry (Lee et al. 2014). The nanocellulose, being renewable, organic and degradable in nature, will not leave the carbon footprint in nature.

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Part III
Nanomaterials in Animal Health

Chapter 17
Recent Trends in Nanomaterials Used in Dairy Industry

Amrita Poonia

Abstract The application of nanotechnology in the dairy industry is going to be a new revolution in the near future. The use of nanostructures in processing products of superior quality and safety and new packaging materials with improved desirable properties are being reported. The properties of bioactive compounds of dairy products can also be improved due to a reduction in the particle size. However, the safety issues about the ill effects of nanotechnology-based dairy foods on human health are of concern. So, there is a need to ensure the safety of nanofoods before commercial utilization. This chapter reviews the various topics like the use of many nano-based delivery systems in dairy products, milk proteins as the perfect natural carriers for nano-encapsulation purposes, nanostructures for the prevention of spoilage causing microorganisms and pathogens in dairy industry. Due to the health concerns, effects of intake of nanoparticles on digestive system, skin, brain, lungs and circulatory system have also been discussed.

Keywords Nanomaterials · Nano-dairy foods · Nanosensors · Nano-packaging · Nanoceuticals

17.1 Introduction

Nanotechnology is the most revolutionary scientific approach in food sector and especially in milk and milk products. It can be applied in different areas of food production, i.e. development of new functional ingredients, their processing at micro- and nanoscale; and in food safety and quality. There are many advantages of using nanomaterials in dairy industry. They can be useful as encapsulating agents for vitamins, antioxidants, flavours, minerals and other nutrients that are important

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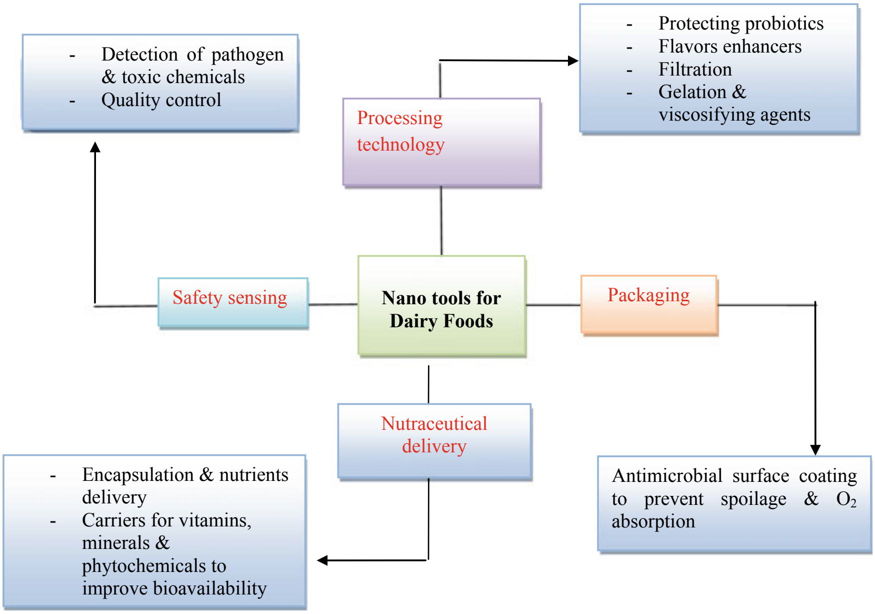

Fig. 17.1 Schematic diagram showing some applications of nanotechnology in different areas of the dairy industry

for fortification of milk and milk products. They also play an important role in the formulation of novel-packaging materials and biosensors for protection against disease-causing microorganisms (Fig. 17.1). Various other areas like protection of milk products from spoilage and oxidation can also be benefited by the application of nanomaterials (Fig. 17.1).

Nanoparticles used in food and dairy industry can be divided into four major groups such as metals, polymers, natural compounds and nano-structured materials. Some biologically active nanomaterials can protect food from opportunistic microorganisms. These different nanoparticles can play different roles through various mechanisms of action (Table 17.1).

Due to the greater surface area of nanoparticles, they are expected to be more biologically active than larger sized particles of the same chemical composition. This provides several perspectives for functional food applications. Various delivery systems used in dairy nanotechnology are depicted in Fig. 17.2. These delivery systems include the biopolymeric nanoparticles, nano-emulsions, nanofibers, association colloids and nanocapsules, etc. These systems will serve up as a vehicle for carrying functional ingredients and their protection from degradation and control the release of functional ingredients (Weiss et al. 2006). All these aspects are discussed further in detail.

Table 17.1 Comparison among main properties of different types of nanoparticles used in dairy industry

Type of nanoparticles	Mechanisms of action	Advantages	Disadvantages
Metal nanoparticles	Can cause the breakdown of negatively charged bacterial cell walls	Antibacterial properties	Non-biodegradable
Polymeric nanoparticles (Fragmented in nanoscale)	• Can be filled with traditional antibiotics and may work as a shuttle to discharge them in close contact to a pathogen • Destabilize bacterial cell walls and homeostasis is disrupted to a lethal extent • DNA transfection vehicles	• Can be grafted onto other materials, potentially enhancing their biocompatibility and degradation making them more useful • No negative side effects on consumers	Nil
Natural compounds (natural polymers or proteins with partial manipulation)	• Nanoparticle added to dairy products for human consumption can boost bioavailability • Enclose nutrients to protect them against degradation in the stomach for maximum absorption	Biocompatible, equally distributes in the body	These particles could have toxic or immunogenic effects if not carefully engineered or properly distributed in a biological system
Nano-structured materials (Synthesized nanoparticles that derived from natural compounds such as lipid and protein-based nanoparticles)	• Designed to carry nutrients or pharmaceuticals through the GI tract for targeted release • Fluorescence can be initiated via light activation or two-photon excitation	Serve as the only functioning unit or carriers for functional groups, such as drugs and nutrients using encapsulation or superficial adhesion	Nil

17.2 Detail Application of Nanomaterials in Dairy Industry

There are various applications of nanoparticles in dairy industry. The main focused areas are (1) enhancement of sensory attributes (colour, flavour and texture) (2) to stabilize the nutraceuticals in food structures (3) targeted delivery of nutrients and

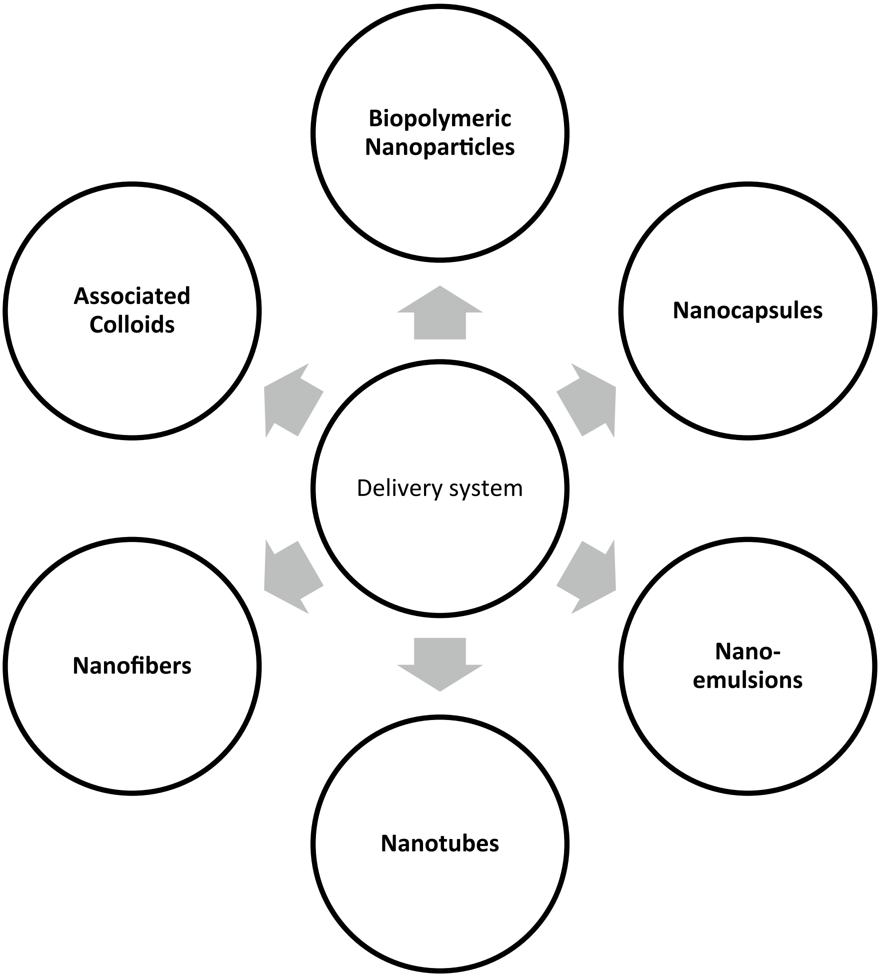

Fig. 17.2 Pictorial representation of nano-based delivery system for different roles in dairy industry

bioactive compounds (4) to consider the safety of dairy foods by packaging or sensing. The various nanomaterials used to achieve these objectives are discussed in detail.

17.2.1 Nano-structured Proteins and Peptides

Due to fulfilling of various criteria like biocompatibility, longer stability, controlled release, encapsulation efficiency, dispersibility in biomatrix, the proteins are considered as perfect candidate for encapsulation purposes (Shin et al. 2015). The milk proteins—caseins and whey proteins (specially β-lactoglobulin, α-lactalbumin, and lactoferrin) can be successfully used for the delivery of nutraceuticals as they can be modified either chemical or enzymatic processes with the objective of changing their structural features (Poonia 2017). The features of these milk proteins can be modified for preparing nanoparticles with new functionality. This potential has been explored, and its use in nano-encapsulation of food materials industry has already received considerable research interest (Poonia 2017). Naturally self-assembled casein micelle in nanoscale act as a delivery tool calcium and protein in dairy-based foods. Similarly, whey proteins bind and transport the hydrophobic biomolecules. The possibility of forming nanotubes and nano-fibrils by various treatments is being explored for delivery of nutraceuticals (Ramos et al. 2017). The use of whey-protein-based edible film for packing of food has been reviewed earlier (Alvarez-Pérez et al. 2017; Rodríguez-Jasso et al. 2017).

Along with complete proteins, nanostructures were formed by self-assembly of peptide β-lg f1-8 in the pH range of 2.0–11.0. Hydrogel formation was studied as a function of pH and resulted in the evidence of a link between hydrogel formation and the charge distribution carried by the peptide structure. Finally, circular dichroism (CD) spectroscopy was used to characterize the effects of peptide concentration (0.4–2.0 mg/mL), ionic strength (0–1 M NaCl) and temperature (20–80 °C) on the secondary structure of peptide β-lg f1-8. Hydrogels were obtained at peptide concentrations above 2.5 mg/mL. Peptide concentration and pH adjustment were shown to trigger self-assembly of β-lg f1-8, but increasing ionic strength had no effect. Heating to 80 °C induced a stronger CD signal intensity due to an increase in solubility of the peptide, whereas only slight changes in CD pattern were found upon cooling to 20 °C. Overall, results emphasize the role of particular molecular interactions in β-sheet self-assembly of peptide β-lg f1-8 and pH-dependent electrostatic interactions occurring between β-lg f1-8 units, which can explain its propensity to self-assembly (Guy et al. 2010).

17.2.2 Nanocapsules

Nowadays, many nanotechnology companies are developing dairy products with different nano-encapsulated ingredients (Prasad et al. 2017). The main function of using nanoscale food additives is to improve flavour, texture, nutritive value of the dairy foods. The purpose of nano-encapsulation of different food products is to formulate the particle size of these nutrients less than 100 nm so that they can cross the stomach wall into the cells rapidly than the nutrients with larger particle size. Nano-encapsulation is defined as a technology to pack substances in miniature making by using nanocomposite, nano-emulsification, and nano structuration and provides final product functionality that includes controlled release of the core. The protection of bioactive compounds, such as vitamins, antioxidants, proteins, and lipids as well as carbohydrates may be achieved using this technique to produce functional foods with enhanced functionality and stability. Nano-encapsulation can make significant savings for formulators, as it can reduce the amount of active ingredients needed (Huang et al. 2010). Probiotics are generally defined as live mixtures of bacterial species and can be incorporated in foods in the form of yoghurts and yoghurt-type fermented milk, cheese, puddings and fruit-based drinks. Encapsulated forms of ingredients achieve longer shelf-life of these products.

17.2.3 Nanoparticles for Antimicrobial Properties

As reviewed previously by many authors, the use of nanomaterials for food packaging has great potential in near future (Bumbudsanpharoke and Ko 2015; Imran et al. 2010; Tsagkaris et al. 2018). Microbial spoilage of dairy products affects the sensory properties of foods and causes some considerable changes. Foodborne pathogens affect the safety and quality of products. The most common spoilage causing microbial group found in dairy products is *Pseudomonas* spp. Two main pathogens found in unpasteurized milk are *Bacillus* spp. and *Listeria monocytogenes*. Growth of yeasts and moulds has also reported in dairy products. In one study, the researchers used the silver-montmorillonite nanoparticles coated on the packaging films to increase the shelf-life of dairy products (Gammariello et al. 2011). Use of modified atmosphere packaging, antimicrobials, different coating materials, bacteriocins and nanoparticles can improve the shelf-life of different types of cheese. Nanocomposite systems can increase the antioxidant and antimicrobial activity of packaging and thus the shelf-life of dairy products. The in vitro test of nanocomposites against the spoilage causing and pathogens in dairy products has discussed in Table 17.2.

17.2.4 Use of Nano-emulsions (NE)

Nano-emulsions consist of a lipid-phase discrete in continuous aqueous phase, with each oil droplet being bounded by a thin interfacial layer consisting of emulsifier molecules. The main characteristics of NE are good stability and thermodynamically stable compared to the normal conventional emulsions. Due to their small size (50–500 nm) and mono-dispersivity, they can be diluted without any change in the droplet size. The mechanism of action of NE and food ingredients (such as proteins, polysaccharides and phospholipids); and process such as homogenization and mixing that are being used extensively in the manufacture of food emulsions are reviewed in some reports (Kumar and Sarkar 2018; Martínez-Ballesta et al. 2018; Weiss et al. 2006). It has been reported that Nestle and Uniliver had developed nano-size emulsion-based ice cream with a lower fat content (Renton 2006; Silva et al. 2012). In one study, nano-emulsion purple rice bran oil (PRBO) was added as a source of natural antioxidants including tocopherol, tocotrienol, and oryzanol in frozen yogurts (FY), which improved the nutritional profile of the product by

Table 17.2 List of nanostructures materials tested against various spoilage and pathogenic microorganisms in dairy products

Nanocomposites	Mode of action	References
L. monocitogenes		
Carbohydrate nanoparticles coated with nisin	Nanoparticles showed persistent antimicrobial effect against plated bacteria, and that was quite longer than uncoated nisin	Bi et al. (2011)
Silver nanoparticles	Active packaging with NPs increased the storage life of Fior di Latte cheese, by controlling microbial growth, without affecting the useful dairy microbiota and the sensory characteristics. This active packaging system can be used to boost the distribution product beyond local borders	Incoronato et al. (2011)
Silver nanoparticles	Shown the significant antibacterial effects on tested foodborne pathogens. Like *E. coli* O157:H7 and *S. typhimurium* was controlled after 6 h of exposure, while *V. parahaemolyticus* and *L. monocytogenes* was controlled after 5 and 7 h of exposure, respectively	Zarei et al. (2014)
Lysozyme-carrying immuno-nanoparticles	As compared to the direct addition of lysozymes nanoparticles were more effective for inhibiting the growth of *L. monocytogenes* in liquid medium	Yang et al. (2007)
Zinc oxide nanoparticles	Efficient growth inhibitors against *Listeria monocytogenes*	Arabi et al. (2012)
P. aeruginosa		
Zinc oxide and titanium dioxide nanoparticles	Both the nanoparticles were effective in avoiding the biofilm formation by *P. aeruginosa*	Vincent et al. (2014)
Zinc oxide nanoparticles	Can inhibit *P. aeruginosa* biofilm formation	Lee et al. (2014)
Silver nanoparticles	Showed bactericidal effect in liquid and solid growth media and it depends on concentration of nanoparticles and number of bacteria present	Kora and Arunachalam (2011)
E. Coli and another spoilage/pathogenic microorganism		
Silver nanoparticles	Nanoparticles synthesized by *Salmonella typhirium* has shown good antibacterial effect against the tested microorganisms	Ghorbani and Soltani (2015)

(continued)

Table 17.2 (continued)

Nanocomposites	Mode of action	References
Nano-encapsulation and nano-emulsion of Carvacrol, Thymol, Linalool and Eugenol	Among the all tested nanoformulations of various essential oils, eugenol has shown highest antimicrobial and antioxidant activity	Khaled et al. (2014)
Chitosan-silver nanocomposite film	Biomaterial-based nanocomposite film produced with chitosan and silver NPs has an outstanding antibacterial property	Pinto et al. (2012), Tripathi et al. (2011)
Nano-emulsion of orange oil	Nano-emulsion-treated cells exhibited loss of its viability within 30 min of interaction	Sugumar et al. (2016)
Zinc oxide nanoparticles	Found to have antibacterial activity against *E. coli* O157:H7 and may distort and damage bacterial cell membrane, resulting in a leakage of intracellular contents and eventually the death of bacterial cells	Liu et al. (2009)

substantially increasing the natural antioxidant content. Peroxide value (PV) (mmol/kg of FY) were 3.55, 2.38 and 2.13 for FY-containing-NPRBO (FYNRO), and frozen-yogurt-with-sodium caseinate (FYSC), and plain-frozen-yogurt (PFY), respectively. While thiobarbituric-acid-reactive-substances (TBARS) (μmoles malonaldehyde/kg of FY) values were 5.2, 4.57, and 4.66 for FYNRO, FYSC, and PFY, respectively. FYNRO had 6.51 (μg/g oil) α-tocopherol, 12.89 (μg/g oil) γ-tocotrienol, and 754.44 (μg/g oil) γ-oryzanol (Sanabria 2012). In one study, the curcumin nano-emulsions (Cur-NEs) were synthesized by using high-pressure homogenization and added in commercial milk samples. The results confirmed that surfactant concentration is the factor that affects particle formation and droplet size. The nano-emulsion was stable for 1 month at room temperature and was effective in oxygen scavenging (Joung et al. 2016).

17.2.5 Nanocoatings

Recently, waxy coating is used extensively for increasing the shelf-life of apples, cheeses and other foods. By using nanotechnology edible coatings in nanoscale (5 nm) can be developed which are invisible to the human eye. These coatings and films are currently used on a large variety of foods, including fruits, meats, chocolate, vegetables, candies, bakery products, cheese and french fries (Cagri et al. 2004; Costa et al. 2018; Flores-López et al. 2016; González-Reza et al. 2018; Rhim 2004; Zambrano-Zaragoza et al. 2018).

Nanocoatings used in dairy products play an important role as they serve as a barrier for moisture, lipid and gas and also act as carriers of releasing agents of colours, flavours, nutrients, antimicrobials and antioxidants (Radha et al. 2014). In nanocoatings, two or more than two layers of nano-laminates are used with nanometer dimensions. These nanomaterials are bonded physically or chemically to each other, and various functional components like antioxidants, flavours, enzymes and colours can be incorporated in these nanostructures. Spray drying technique is used for the nanocoatings with nano-laminates. Some researchers have reported that use of nano-laminate coatings for the preservation of Coalho cheese and found it effective to increase the shelf-life of cheese than the uncoated cheese due to gas barrier and antibacterial properties of nanocoatings (McClements 2015; Medeiros et al. 2014). In processing of milk, the use of nanocoatings has been studied to reduce milk spoilage inside gasketed plate heat exchangers. The results of study have indicated that polyurethane-coated plates showed a significant reduction in milk fouling when compared with uncoated stainless steel plates (Kananeh et al. 2010).

17.2.6 Nanofibers for Various Application

Nanofibers with diameters from 10 to 1000 nm make them ideal for serving as a platform for bacterial cultures as well as structural matrix for artificial foods. Kanjwal and co-workers studied the photocatalytic degradation of dairy effluent and methylene blue using zinc oxide nanofibers (ZnO NFs), nickel oxide nanofibers (NiO NFs) and composite zinc oxide–nickel oxide nanofibers (ZnO–NiO NFs) (Kanjwal et al. 2015). The developed nano-membranes were characterized by SEM, TEM, XRD and ultraviolet studies. It was reported that pristine nanofiber membranes were smooth and continuous with 400 nm diameter, and their nanofibrous morphology was same after calcination at 600 °C for more than 3 h. It was then used for photocatalytic degradation of dairy effluent and methylene blue (MB) dye. NiO nanofibers and ZnO nanofibers showed a maximum degradation of 70 and 75% in dairy effluent and 50 and 60% in MB dye, respectively, after 3 h. It was concluded that the nanofibers' morphology strongly enhances the surface activity of the ZnO–NiO photocatalyst at room temperature (Kanjwal et al. 2015).

Similarly, Kanjwal and co-workers produced ZnO nanofibers by electrospinning technique and surface coated on silicone elastomer substrate (diameter: 10.0 mm; thickness: 2.0 mm) by a dip-coating method. The developed hybrid nanoporous matrices were investigated, and the study revealed that the surface morphology of electrospun nanofibers remained intact by the dip-coating technique and showed high water flux of 9407 L/m(2)h, 38% removal rate of dairy effluent (DE) and 2298 mL/g h rate of hydrogen production (Kanjwal et al. 2016).

The polyethylene oxide nanofibers containing nisin-loaded poly-γ-glutamic acid/chitosan (NGC) nanoparticles was developed and used to inhibit the growth of bacteria in cheese. The NGC nanoparticles at 5 mg/mL of nisin had desirable polydispersity, zeta potential, encapsulation efficiency and load capacity. NGC nanoparticles-embedded polyethylene oxide nanofibers displayed satisfactory antibacterial activity against *L. monocytogenes* on cheese, without affecting the sensory attributes of cheese (Cui et al. 2017). In another study, urea-sensing platform was fabricated using polymeric electrospun nanofibers of polyamide 6 (PA6) and polypyrrole (PPy) deposited onto fluorine-doped tin oxide (FTO) electrodes, which were then modified with zinc oxide nanoparticles (ZnO). It was reported that the material showed excellent properties for the immobilization of urease enzyme, conferring the FTO/PA6/PPy/ZnO/urease electrode high sensitivity for urea detection within the concentration range between 0.1 and 250 mg dL^{-1} with a limit of detection of 0.011 mg dL^{-1} (Migliorini et al. 2018). Both the results proved the potential of polyethylene oxide nanofibers in various aspects of milk production.

17.2.7 Nanoceuticals

Dairy products added with nanoceuticals are becoming more popular (Chen et al. 2006; Mozafari 2006). Carotenoids, lycopene and other nutraceuticals can be added to dairy-based products to improve their bioavailability. Different types of nanoceutical products with nanoclusters, nanocages and nanodrops play the role of delivery vehicles in dairy products. By reducing the particle size of the bioactive compounds, solubility, biological activity and availability can be improved. It has been reported that the application of nanotechnology increases the stability of nutraceuticals during heat processing and storage (Chen et al. 2006). Different dairy supplements containing nanoparticles like carotenoids, omega-3 fatty acids, some probiotic bacterial species, minerals, lycopene and vitamin D_2 (Neethirajan and Jayas 2011). Functional butter was developed using nano-sized herbal supplements like polysaccharides, pectin, inulin, cryopowders of red beets, carrots and black currants buds with surface-active properties. During the scanning electron microscopy (SEM) of butter, they observed that addition of a small quantity of pectin decreases the structural elements of butter to 5–25 times and is in the range of 1–100 nm. The nature and properties of the herbal additive significantly affected by the formation of nanostructure of butter and morphology of its nano-elements. Nanoparticles of silver and gold are available as supplements to avoid the accretion cholesterol in the body. Various nutraceuticals added in the carriers are β-carotene, lycopene and phytosterols. Synthetic lycopene has been avowed as a generally recognized as safe (GRAS) under US FDA procedures (Ravichandran 2010).

17.2.8 Nanopackaging

Nano-packaging in dairy products is used to protect content and enhance the storage life of the dairy products. The commonly and frequently reported nanoparticles in packaging are metals like copper, zinc oxide, silver and titanium

Table 17.3 Application of nanoparticles in packaging system to extend the storage of dairy products

Material used	Product	Tested microorganisms	References
Copper nanoparticles	Dairy products	*Pseudomonas* spp	Longano et al. (2012)
Copper nanoparticles	Fiordilatte cheese	*Pseudomonas* spp	Conte et al. (2013)
Silver nanoparticles loaded in the edible coating	Fiordilatte cheese	*Pseudomonas* spp, Enterobacteria	Mastromatteo et al. (2015)
1% nanosilver and 0.1% titanium dioxide	Soft cheese and milk powder	Enterobacteria	Metak and Ajaal (2013)
ZnO nanoparticles coated on polyvinyl-chloride-based film	Dairy products	*E. coli* *S. aureus*	Li et al. (2009)
Zinc nanoparticles coated on packaging film	Butter	–	Contreras et al. (2010)
TiO_2 used in HDPE-based food packaging	Soft ripened cheese	Degradation of activity towards organic compounds	Gumiero et al. (2013)
Agar hydrogel with silver nanoparticles	Fior di Latte cheese	–	Incoronato et al. (2011)
Chitosan/poly (vinyl alcohol)/titanium nanoparticles (CS/PVA/TiO2 nanocomposite)	Soft white cheese	*Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli* and *Candidia albicans*	Youssef et al. (2015)

dioxide. A novel nanocomposite coating of polylactic acid (PLA) embedded with bioactive copper nanoparticles (CuNPs) has exhibited excellent antibacterial activity in Fior di latte cheese stored at 4 °C for 9 days (Conte et al. 2013). Shelf-life of dairy products can be extended by using biocompatible and biodegradable coatings. In case of *Coalho* cheese, five alternate layers of alginate and lysozyme were assembled to extend its shelf-life up to 20 days (Medeiros et al. 2014). All these metals show considerable antimicrobial properties when used for the packaging of dairy products Table 17.3.

17.2.9 Use of Various Nanosensors in Dairy

Biosensors are being used in every area of food technology, starting from monitoring of raw materials, processing, packaging, shelf-life and judging the quality of food during long-term storage. Nanosensors can be used to track the quality (external and internal conditions) of the milk and milk products throughout the supply chain. They are also used to detect the bacteria and other contaminants on the surface of a food at packaging place. Some gas sensors can translate the chemical interactions between particles on the food into a response signal (Omanović-Mikličanina and Maksimović 2016). They are used to detect preservative food contaminant in dairy products. In dairy industry, the nanosensors are used to estimate the antibiotics residual amount in milk and milk products (Poonia et al. 2017). General applications of nanosensors are highlighted in Box. 1

Box 1. Applications of Nanosensors in Dairy Industry

Cost-effectiveness: Nanosensors are rapid and high-throughput detection, simple and cost-effective, less power requirements, easier recycling and the unnecessity of exogenous molecules or labels.

Quality assurance: Nanosensors can track the food processing line to assure the quality of food. They can also check the product tempering and able to track ingredients and products through the processing chain and commercialized products.

Monitoring and controlling specific stages of milk processing: Nanosensors can also monitor and control the various stages of a milk-processing unit (Sekhon 2010).

Food safety: Gasses produced with off flavours can be detected by nanosensors with plastic packaging. When a food spoil, the packaging materials automatically change colour itself and alert us about the food spoilage. Nanosensors with silicate nanoparticles reported to reduce O_2 in the package and retain the freshness of food by reducing the flow of $O_{2.}$

Detection of foodborne pathogens and microbial load: *Salmonella typhymurium*, *Eschirichia coli, Listeria monocytogensis* cells can be detected using aptasensors. DNA biochips are used to detect pathogens and other harmful bacteria in meat and seafoods.

Detection of drugs and heavy metals: By using aptasensors antibiotics, drugs and their residues and heavy metals like Hg^{2+}, A^{s3+} and Cu^{2+} can be detected.

For intelligent food packaging: Nanosensors used in packaging can assess the internal and external conditions of food products through the supply chain. The nanosensors are used into the packagings to indicate the storage conditions. Some microbes and physical parameters such as pathogens, temperature, pH, humidity, oxygen content, toxins and freshness are assessed by finding the fermented end-product of the food. Example: OxyDot® is a commercially available nanosensor being used for quantitative analysis of sealed drink product.

By using the nanosensors, very less concentration, i.e. 1×10^{-9} M, of antibiotics could be detected by general colour change. The occurrence of aflatoxin M_1 in milk is very common and specially found in milk from animals fed with aflatoxin B_1 contaminated feed. The use of gold-nanoparticles labelled aflatoxin M_1 conjugate is very beneficial. It has been reported that a very small amount, i.e. 27.5 mg L^{-1} in a sample solution was possible to detect (Zhang et al. 2015).

Brucellosis is an infectious disease caused by *Brucella* spp. in cattle. It can spread to human by the consumption of unpasteurized milk and milk products or by contact with the infected sensory organs. It is an economic concern in many parts of the world as it results in reduced productivity, abortions, weak offsprings and major impediments for trade and export of livestock. Human brucellosis is a severely debilitating disease that requires prolonged treatment with the use of several antibiotics which involves considerable medical expenses and affects the working efficiency. The detection of Brucella IgG antibodies in milk samples and used antigen-tagged fluorescent silica nanoprobes has been reported (Vyas et al. 2015). The developed sensor was very sensitive, accurate, and specific and requires a small amount of sample, i.e. 50 μL within a short duration of 10 min. Another study reported the application of copper-doped magnesium oxide (MgO) as an efficient matrix to fabricate electrochemical immunosensors for the detection of *Brucella abortus*. There was a detectable change in the redox peak currents with *Brucella abortus* in the presence and absence of antibody (Khan et al. 2017).

In one study, the iron oxide nanoparticles and carbon nanotubes were used for the detection of H_2O_2 in milk samples. The electrochemical biosensor had very good performance with a detection limit of around 3.7 nM (Thandavan et al. 2015). One sensor for the detection of protein content in commercial fermented milk was developed, where the detection limit was in the range of 0.0714–1.25 mg/mL (Deng et al. 2015). In another study, a novel electrochemical immunosensor for the detection of staphylococcal enterotoxin B in milk was reported. It was reported that the sensor shows good repeatability and very sensitive with the detection limit of (0.017 ng/mL) (Wu et al. 2015). Electrochemical sensors were also used for the detection of melamine in milk and milk products. In this sensor, the graphite electrode was impregnated with paraffin and modified with melamine, silver nanoparticles, chitosan and polyquercetin. The detection limit of this sensor was 1.3 nM in the real samples (Jin et al. 2011).

Scagion and colleagues developed a novel and portable impedimetric e-tongue based on gold inter-digitated microelectrodes (IDEs) modified with polyamide 6/polyaniline (PA6/PANI) electrospun nanofibers and used them to detect tetracycline (TC) residue in fat and skimmed milk samples. The e-tongue was able to identify the presence of tetracycline (TC) residues (from 1 to 300 ppb) in fat and skimmed milk. The results obtained showed the ability of the approach of modifying IDEs with conducting electrospun nanofibers to be used as sensing units in the e-tongue and the purpose was to analyse complex matrices like milk without any prior pre-treatment (Scagion et al. 2016).

The electronic nose and electronic tongue are performing similar functions as the human sensory organs. They are used in every area of food technology, starting from the monitoring of raw materials, processing, packaging, shelf-life and judging the quality of food during long-term storage. An ion-mobility-based e-nose

(MGD-1) was reported for differentiation hardness in cheese samples and discriminate them based on their ripening time or origin (Gursoy et al. 2009). In another study, an α-Mos e-nose with three metal oxide chambers containing 18 sensors was used to determine the shelf-life of milk (Labreche et al. 2005). At ambient or refrigerated temperatures, this sensor monitored the bacteria growth in the milk. Similar kind of e-nose was also used for studying the milk-flavouring profiling. They studied five different commercial samples along with one self-made enzyme-induced milk-flavouring prepared by lyophilized milk fat (Wang et al. 2010). The results reported that the e-nose could distinguish the difference among all the milk-flavourings as well as between the natural and enzyme-induced milk-flavourings that were not that distinguishable in sensory tests. These results were validated by solid phase micro-extraction gas chromatography-mass spectrometry (SPME GC-MS) (Wang et al. 2010).

In past, potentiometric e-tongue and partial least squares-discriminant analysis (PLS-DA) was used to differentiate milk samples that were originated from different producers by utilizing an array of microelectrodes (Ag/AgCl) fabricated from epoxy-glass laminate and polyvinyl chloride (PVC) membranes (Ciosek and Wróblewski 2008). In another study, the changes in probiotic fermented milk during storage, and their classification based on flavour has been predicted by the use of a potentiometric sensor array. The predictions were assured to be correct by comparing these results with the results of human sensory panel evaluation. The e-tongue system consisted of seven sensors and an Ag/AgCl reference electrode (Hruškar et al. 2010). The e-nose was highly accurate (97%) in differentiating the plain probiotic fermented milk and lowest for apple-flavoured. The statistical analysis revealed the highest correlation in results of both e-nose and human sensory study was found in forest-fruit-flavoured fermented milk. A disposable voltammetric e-tongue was designed for the detection of hydrogen peroxide adulteration in milk. The e-tongue was fabricated with gold CD-R and copper sheet substrates and sensing elements in this tongue were gold, copper and gold surface modified with a layer of Prussian Blue (Paixão and Bertotti 2009). The statistical analysis confirmed the utilization of this sensor for classifying various milk samples based on characteristics like pasteurization process and adulteration of H_2O_2. In another study, an e-tongue containing 36 cross-sensibility sensors was used to evaluate the five sensory standards. It was highly sensitive to acid, salty and umami tastes but had lower recognition performance for bitter and sweet tastes. This capability was successfully used for the detection of cow milk mixing in goat milk (Dias et al. 2009). Newman et al. (2015) studied whether a commercially available electronic tongue (e-tongue) could be used to identify sweeteners and flavours which reduce bitterness perception in model beverages containing Sodium caseinate hydrolysates (NaCaHs) and reported that e-tongue is an effective tool for measuring the reduction of bitterness of NaCaHs due to different sweeteners. The results also showed good agreement between the e-tongue and sensory panel in the measurement of bitterness and sweetness in sweetened NaCaHs suggesting that the e-tongue may be a useful device for the selection of sweeteners as bitterness masking agents in NaCaHs (Newman et al. 2015).

The working principle of another promising sensor, i.e. optical biosensor relies on the detection of the change in the optical signal with different spectroscopic measurements. Nanomaterials including metals, magnetic NPs, carbon-based nanostructures, latex nanoparticles and liposome nanoparticles have been used in SPR sensing system for the detection of mycotoxins, antibiotics and various pathogens (Zeng et al. 2014). Liu and co-workers reported the fabrication of optosensor with surface-modified CdSe and ZnS quantum dots with the silane group and conjugated with the methylacrylate functionalized molecularly imprinted polymer. They used it for the detection of Nε-carboxymethyllysine (CML) in the milk product and the concentration of the CML was linearly correlated with the fluorescent quenching of the quantum dots (Liu et al. 2016).

A new antibody/gold nanoparticle/magnetic nanoparticle nanocomposite (antibody/AuNP/MNPs) were used for the detection of the foodborne pathogen like *S. aureus* in milk. The nanocomposites were synthesized by coating the MNPs with bovine serum albumin (BSA) then adsorbing the AuNPs and anti-*S. aureus* antibodies on their surface (Sung et al. 2013). It was reported that the detection limits of this colorimetric sensor were 1.5×10^3 and 1.5×10^5 CFU for *S. aureus* in PBS and the milk sample, respectively. When compared with other pathogens such as *Escherichia coli*, *Listeria monocytogenes* and *Salmonella enteric,* the sensor showed high specificity for *S. Aureus* and require only 40 min to obtain the results. This strategy can provide an easy, convenient and rapid sensing method for a wide range of pathogens (Sung et al. 2013).

Dopamine-stabilized silver nanoparticles (AgNPs) as a colorimetric reader were used to detect melamine in raw milk. This one-step assay is simple, rapid and highly sensitive. The colour change is quantitatively correlated with the concentration of melamine in the range of 10 ppb to 1.26 ppm, which is below the safety limit in China (1.0 ppm) and EU (2.0 ppm). The coexisting substances including phenylalanine, DL-leucine, L-glutamate, sulfanilic acid, Mg (2+), galactose, lysine, urea and glucose do not affect the determination of melamine (Ma et al. 2011). A low-cost visible-near infrared (400–1100 nm) sensor was calibrated and validated for on-line monitoring of fat and fatty acids content in milk during the manufacturing process of milk. The measurement range of the sensor was 400–1100 nm & it covers the visible range (400–780 nm) and the short-wave near infrared (780–1100 nm) (Villar et al. 2012). A novel, selective and eco-friendly sensor for the detection of tetracycline was developed by grafting imprinted polymers onto the surface of carbon quantum dots and the detection limit of tetracycline was 5.48 nM. This will also offer a new way of thinking for rapid analysis in complex samples (Hou et al. 2016).

Electrochemical nanosensors are the most commonly and universally accepted sensors. The working principles of electrochemical nanosensors rely on chemical reactions between nanofabricated chemical biomolecules and target analyte. These nanosensors are highly sensitive, compatible, less power consumption, economical, simple and low detection limits. Duran and Marcato (2013) studied the application of electrochemical nanosensors in the detection of antibiotics, pesticides, heavy metal and preservation in food and agriculture sector. A sensitive imprinted electrochemical sensor based on cubic gold nanoparticles (cAuNPs) involved in

2-aminoethanethiol (2-AET) functionalized graphene oxide (GO) modified glassy carbon (GC) electrode was developed for determination of tyrosine (Tyr) in milk samples. The detection limit were reported in milk as 1.0×10^{-9} to 2.0×10^{-8} M and 1.5×10^{-10} M, respectively (Yola et al. 2015). A novel piezoelectric cantilever sensor was developed for the detection of *Listeria monocytogenes* (LM) in milk. Detection sensitivity of LM at a concentration of 10^2/mL was achieved, by incorporating a third antibody binding step, which is an order of magnitude smaller than the infection dose (<1000 cells) for LM (Sharma and Mutharasan 2013).

17.3 Nanomaterial-Based Foods and Their Safety

Application of nanotechnology in dairy processing and production including packaging has become very popular these days. The consumers are also exciting to have these foods. But there is a serious concern about the safety of these dairy-based nanofoods. Due to the nano-size of the material, there is an increase in the contact surface area, which leads to toxic effects in the body. But there is a lack of regulation and knowledge about these nanomaterials. Though, a variety of food products are available in the market. Most of the researchers and research committees found that this technology is useful, but new researches may be required to ensure the safety of these nanomaterials (Cockburn et al. 2012). There are only few government agencies reported regarding the regulatory framework for the use of nanotechnology (Handford et al. 2015). There is a need to develop precise framework for general application in dairy-based nanofood industry. In some countries, nanofoods have been commercialized and are reported in the Consumer Products Inventory of Project on Emerging Nanotechnologies (PEN) (http://www.nanotechproject.org/cpi/) (Handford et al. 2015). But still, there are no legal labelling requirements of nanomaterials used in dairy foods.

There are many body systems like respiratory system, digestive system and skin through which the nanoparticles can enter the human body (Fig. 17.3). The ingestion of nanoparticles may cause increased oxidative stress, production of free radicals leads to DNA mutations and fatal to human beings. The need for safe use of dairy products has been reported by Joye et al. (2014). In vivo and in vitro tests are needed to know their absorption, metabolism, distribution and toxicological profiles. More researches are needed to find out long-term health risks and biological effects.

Active and intelligent packaging is used which includes advances in delayed oxidation and controlled respiration rate, microbial growth, and moisture migration. Few more examples of this are carbon dioxide absorbers/emitters, odour absorbers, ethylene removers and aroma emitters, while intelligent packaging includes time–temperature indicators, ripeness indicators, biosensors and radio frequency identification. Until 2004 in Europe, there was a legislative lack for this kind of

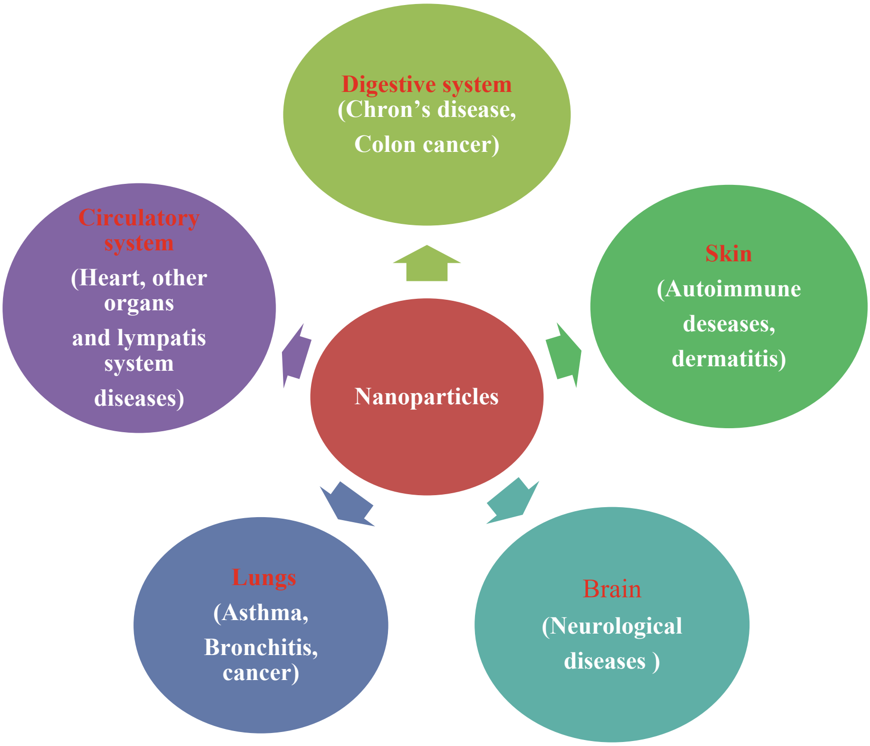

Fig. 17.3 Pictorial representation showing possible harmful effects of nanoparticles on human health

packaging decreasing their penetration in the EU market (Restuccia et al. 2010). It has been reported that there is a need for better communication among the scientists, dairy industry, government agencies, and the consumers about these foods (Handford et al. 2015).

17.4 Prospects

As the research in food nanotechnology is increasing continuously and raises public concerns about the safety of the products of nanotechnology for human consumption. So, there is a need of a broad assessment of (1) potential risks to human health before introducing the nanofood products in the market (2) universal guidelines that is specifically developed for the safety assessment of nanomaterials in dairy foods before being approved for its use (3) more studies are required to be done regarding the regulations about the impacts of these nanomaterials on human and environmental health to assure the food safety.

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Chapter 18
Drug Encapsulation and Nanocarriers for Targeted Delivery in Animals

Utkarsh Jain and Nidhi Chauhan

Abstract Recent years more and more research is going on nanotechnology and associated science, which mainly focused on human welfare and clinical field. Different nanocarriers have not only used in targeted drug or nucleotides or proteins delivery, but they also demonstrated upgraded advancement over conventional techniques. Therefore, we have divided this chapter into four parts, in which the first part completely introduced nanocarriers and their laboratory-based synthesis methods. Second part explained the characteristic of nanocarriers along with merits and demerits of different nanocarriers in use in several severe disorders. Third part is important elaborates regarding the type of nanocarriers, their use in drug or nucleic acid delivery in different disorders and most importantly commercialized therapy in different diseases and their current status in the market. Fourth and last part of chapter mainly focused on rules and regulations of nanomedicine preparation and characterization in Indian scenario, along with future concern in reference to use of nanocarriers in complex disorders and their potential growth in the clinical field.

Keywords Drug encapsulation · Nanocarriers · Targeted delivery · Nanomedicine · Regulations · Lipid nanoparticles

18.1 Introduction

Nanoscale technology, a multidisciplinary scientific undertaking, involves creation and utilization of materials, devices, or system on nanoscale. This technology is expected to create innovations and play a critical role in various biomedical fields; it has also been developed for a wide range of applications which is required for the inception of improved and modified scientific scenario in medical sector comprised

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of prevention, diagnosis, and treatment of diseases (Emerich and Thanos 2003). The prominent evolution of nanotechnology regime can allow evolution and commercialization of a novel range of biologically active macromolecules, which requires a highly explicit intracellular delivery for their action (Kakkar et al. 2017; Sapsford et al. 2013). These advancements in the nanotechnology are eluded by National Institutes of Health (NIH) as nanomedicines (Marchesan and Prato 2013). These medications have the capability to transform subatomic revelations emerging from proteomics and genomics into a potential advantage for patients. Nanoparticles are capable to mock the biological entities and also have the capability to modify the biological responses generated by them. These gadgets incorporate various nanostructures such as nanosized silicon chips (Sutradhar and Sumi 2016), polymeric nanoconstructs (Hunter and Moghimi 2017), nanomachines (Kumar et al. 2018), functionalized carbon nanotubes (Li et al. 2017), and nanofibres (Deepak et al. 2018) to deliver the biological entities, such as peptides or proteins (Ray et al. 2017), drug (Zhou et al. 2018), and nucleic acid (Liu et al. 2017b). These devices are also utilized in the biosensing and diagnostic sector (Salata 2004).

Over the period of 20 years, the fundamental research in nanoscience utilizes applications of nanotechnology to profit society. To produce nanostructures, which are capable to impart medical benefits, guided bottom-up approach is utilized. In this approach, formulated macromolecular components are instructed to react with one another and form a self-assembled complex structure with the help of external stimuli (Sharma et al. 2018; Whitesides et al. 2005). Drugs, to be delivered, can be either encapsulated in the core of nanoparticles or can be coated on their exterior.

Drug delivery implies to technologies of formulations, system, and approaches for transferring an active pharmaceutical ingredient in the body, which is also required, to safely acquire the appropriate therapeutic effect. The formulation of drug delivery nanoparticle initially requires a nanostructure such as drug conjugated polymers, dendrimers, liposomes, and polymeric micelles (Igarashi 2008; Mahmud et al. 2007; Svenson and Tomalia 2012; Torchilin 2004). The transport of drug delivery vehicles synthesized by nanotechnology to the place of action can be acquired by three methods, namely active targeting, physical targeting, and passive targeting (Bertrand et al. 2014; Maeda 2001; Ruoslahti 2002; Yuan et al. 1995). To trigger any of the methods, the alterations are required in temperature, pH, or their combination (Joshi et al. 2017; Liu et al. 2017a). To formulate an effective nanostructure preparation, additive effects of surface chemistry, shape, patient-specific information, size, and other criteria need to be well understood (Haddish-Berhane et al. 2007).

18.2 Delivery Vehicles Containing Nanostructures

The weapons for novel drug delivery system are formulated by confining the drug in cavity lined by a membrane, made up of polymer. Nanocapsules resemble vesicular systems and are biodegradable, and capable of delivering a potent drug (Reis et al. 2017; Rizvi and Saleh 2018). Nanospheres resemble matrix systems. These are formulated by the uniform physical dispersion of the drug (Sahoo et al. 2017). Nanomedicine is the medical application of nanotechnology which is composed of the entities >200 nm. Conventionally, the desired drug is entrapped, dissolved, attached, adsorbed, or encapsulated onto or into a nanostructure-based matrix (Liu et al. 2017a). Nanoparticles, nanospheres, and nanocapsules having different properties and release characteristics are constructed by different preparation methods, in order to achieve appropriate transporter encasing of the drug (Barratt 2000; Couvreur et al. 1995; Pitt et al. 1981). The nanocapsules have pulled in extraordinary intrigue in light of their protective encasing, which is typically pyrophoric and oxidizes, effectively (Marturano et al. 2016). They are remedially more invaluable over free medications; in any case, the inert transporter materials serving as a major segment (for the most part over 90%) have low medication stacking substance and in this manner, require the utilization of parenteral excipients (Shen et al. 2010).

Their fundamental merits are to be specific maintained discharge, incremental medication selectivity and adequacy, change of medication bioavailability and mitigation of medication lethality (Blanco et al. 2015; Pathak and Thassu 2016; Rizvi and Saleh 2018; Tyagi and Subramony 2018). Nanocapsules, which are of submicron size, when managed intravenously, reach the destined target site and discharge the encased drug. Polymeric nanoparticles are named nanocapsules (Jäger et al. 2007) when they comprised of a polymeric wall made out of macromolecules, nonionic surfactants, phospholipids (Béduneau et al. 2006; Mohanraj and Chen 2006) and an oil center (da Fonseca et al. 2008). These are synthesized by two strategies: the interfacial nanodeposition and interfacial polymerization (Nilewar et al. 2017). Nanocapsules hold the biomedical intrigue since they can be utilized for the controlled discharge and focusing of medications against the protection of outside cells, proteins and catalysts, and so forth (Diaspro et al. 2002).

18.3 Characteristics of Nanoparticles Required Facilitating Drug Delivery

18.3.1 Dimension of the Nanoparticle

Nanoparticles (NPs) are minute particles ranging in size from 1 to 100 nm. NP size depicts biological fate, targeting ability, toxicity, and in vivo distribution of these particles. Particle size also determines drug release, drug loading, and stability.

NPs possess advantageous characteristics in comparison to their bulk counterparts (Panyam and Labhasetwar 2003). NPs show enhanced rate of uptake by the cell and can access various intra- and inter-cellular targets. They can pass through the blood–brain barrier followed by endothelium tight junctions via hyperosmotic mannitol (Ceña and Játiva 2018; Soni et al. 2016). Indeed, even little size contrasts might be of impact for the actual dispersion and in this manner bioavailability (Fang et al. 2006; Fishbein et al. 2001; Saez et al. 2000; Shim et al. 2004; Zhang et al. 2004).

For liposomes with sizes >100 nm the rate of clearance by the mononuclear phagocytic framework expanded with expanding the size, while for sizes beneath 100 nm charge was more imperative (Senior et al. 1991; Senior and Gregoriadis 1982). Mannitol gives assisted delivery of the drug in case of severe incurable diseases such as brain tumor (Desai et al. 1997). Nanoparticle uptake by Caco-2 cells varies as follows, 100 nm NPs elicit 2.5 times and 6 times enhanced rate of uptake in comparison with 1 and 10 μm particles, respectively (Desai et al. 1997). Particles with smaller dimensions, i.e., enhanced surface area-to-volume ratio, further facilitate rapid release of drugs. However, smaller particles are prone to aggregation in the period of storage, dispersion, and transport. Degradation of polymers is also governed by particle size (Redhead et al. 2001).

18.3.2 Nanoparticles Surface Characteristics

Nanoparticles employed in biomedical applications ought to be biocompatible, non-lethal, non-detectable by the immune system, and prompt least side effects. To fulfill these requisites, it is suggested that the surface is altered by hydrophilic polymers or different moieties. Nanoparticles (<100 nm) modified using hydrophilic surfaces can skip the reticuloendothelial framework (RES) uptake (Cammas et al. 1997; Löbenberg et al. 1998), stay in the blood dissemination at high concentration (Dunn et al. 1994; Stolnik et al. 1995), lastly reaches to the objective organs, tissues, or cells. For site-particular delivery, the nanoparticle surface should be altered by functional ligands having enhanced affinity toward the infection site. The functional ligand can control the transport of nanoparticles to the target site.

The interaction of the drug and the nanocarrier alters the biodistribution profile of the drug and due to the fact that the distribution is facilitated via MPS (mononuclear phagocyte system) comprised of bone marrow, liver, lungs, and spleen (Palomba et al. 2018; Zhou and Dai 2018). In case of intravenous insertion of nanoparticles, these are identified via the immune system of the host and destructed via the action of phagocytes (Müller et al. 1996). The hydrophobicity of nanocarriers is a key determinant of their transport, toxicity, and fate which depicts the extent of binding of blood cells to the surface of nanoparticles (Ahmad Nor et al. 2015; Reis et al. 2017). Thus, hydrophobicity influences the in vivo future of nanomaterials. In order to increase the likelihood of successful drug targeting, circulation of nanoparticles needs to be maximized and opsonization needs to be minimized. It can be accomplished by the exterior modification on nanoparticles surface by hydrophilic polymers/surfactants or biodegradable copolymers having hydrophilicity. The nanoparticle's exterior charge is defined by zeta potential which is important to determine the stability, as surface charge prevents the aggregation of nanoparticles (Couvreur et al. 2002; Olivier 2005).

18.3.3 Loading of the Drug

For an effective nanodelivery system, it should possess enhanced drug loading capacity which reduces the administration loading quantity. For an efficient nanodelivery system, it is imperative to have high drug-carrying potential. In order to accomplish this, the matrix material required for the delivery needs to be reduced. Nanoparticles (NPs) drug loading is one of the keys defining characteristics of a nanoparticle formulation. Loading of the drug requires the incorporation during nanoparticle formulation. One of the methods of drug loading is absorption/adsorption. In this method, the drug is absorbed after production of the nanoparticle by incubating the drug (high conc. solution) and nanocarrier together (Fournier et al. 2004). The loading of drugs, such as proteins and macromolecules, in nanocapsules at their isoelectric point shows maximum loading efficiency (Govender et al. 2000, 1999; Panyam et al. 2004).

18.3.4 Release of the Drug

The release rate of the drug is based upon solubility, desorption, diffusion through the nanomatrix, and nanomatrix degradation (Kamaly et al. 2016; Rizvi and Saleh 2018). Drug having a predetermined rate of release is required to keep constant drug concentration for a particular duration of time with least side effects. If the drug diffusion is rapid in comparison with the degradation of matrix, then the drug release is mainly affected by the diffusion processes. The rapid drug release is initiated because of the loosely bonded drug on nanoparticles large surface (Magenheim et al. 1993). Additionally, the drug release is also governed by the ionic interactions occurred between drug and other formulating ingredient (Chen et al. 1994). Different methodologies for the examination of the release of the drug are side-by-side diffusion cells, reverse dialysis diffusion, agitation with centrifugation, and ultrafiltration (Daneshmand et al. 2018; Skoczen and Stern 2018).

18.3.5 Targeted Drug Delivery

Targeted drug delivery system refers to a drug transportation system where the target can be fulfilled by the strategies, namely active, passive, inverse, dual, and twofold (Sahoo et al. 2017). Active targeting includes the adjustments of the medication bearers with the goal that the substances are conveyed solely to the site compared to which the transporter is architected. Passive targeting uses the regular course of biodistribution of the bearer, and the medication is joined into a nanoparticle. This encapsulated drug reaches the target organ, passively (Lamprecht et al. 2001; Maeda 2001; Maeda et al. 2001; Sahoo et al. 2002). The inverse targeting is focused on endeavors are made to stay away from latent take-up of colloidal transporter by RES, and thus, the procedure is referred to as inverse targeting. To accomplish inverse targeting, RES typical capacity is smothered by pre-infusing huge quantity of clear colloidal macromolecules. This approach prompts immersion of RES and concealment of defense component. This kind of targeting is a viable way to deal with the target drug(s) to non-RES organs (Singh and Lillard 2009).

Dual targeting is focused on carrier atoms, which itself have their own particular therapeutic action and therefore increment the restorative impact of medication (Yang et al. 2011). For instance, a carrier particle having its own particular antiviral action can be stacked with antiviral medication and the net synergistic impact of medication conjugate was analyzed. In twofold targeting, the transient and spatial procedures are consolidated to focus on a carrier framework (Gao et al. 2014; Sun et al. 2017). Spatial position identifies with focusing on medications to particular cellular compartments, cells, tissues, or organs. Temporal position identifies to controlling the rate of medication conveyance to the target site (Bhargav and Madhuri 2013).

18.4 Merits of Nanoparticle Drug Carriers

Polymeric nanoparticles possess the merits of being utilized as drug carriers are extremely stable, elevated carrier capacity, association feasibility with hydrophilic and hydrophobic substances (Herrero-Vanrell et al. 2005; Vauthier et al. 2003). These particles can be tailored in terms of their features and chemistry of the surface (Kreuter 2014; Moghimi et al. 2001; Panyam and Labhasetwar 2003; Panyam et al. 2003). It has been found that nanocarriers can accumulate specially to tumors, inflammation sites, and at antigen inspecting destinations by prudence of the improved penetrability and retention (EPR) impact of the vasculature (Shi et al. 2017; Wang et al. 2017). Once gathered at the target site, hydrophobic biodegradable polymeric nanoparticles can go about as an area depot of the medication subordinate upon the construction of the carrier, giving a source to a steady supply of encased drug(s) at the contamination site, e.g., solid tumors

(Blanco et al. 2015; El-Sawy et al. 2018). These frameworks when all is said in done can be utilized to give focused on (cell or tissue) conveyance of medications, enhance bioavailability, support arrival of medications, or solubilize drugs for fundamental conveyance. This technique can be changed in accordance with secure therapeutic administrators against enzymatic debasement (i.e., nucleases and proteases) (Ge et al. 2002). Along these lines, the advantages of using nanoparticles for sedate transport are an outcome of two essential crucial properties: minimal size and use of biodegradable materials (Pathakoti et al. 2017; Sahoo et al. 2017). Nanoparticles, in perspective of their little size, can extravasate through the endothelium in blazing goals, epithelium (e.g., intestinal tract and liver), tumors, or enter microcapillaries (Blanco et al. 2015; Nakamura et al. 2016; von Roemeling et al. 2017). All things considered, the nanosize of these particles considers capable take-up by an arrangement of cell sorts and particular solution gathering at target regions (Desai et al. 1997; Panyam and Labhasetwar 2003; Panyam et al. 2003). Numerous examinations have shown that nanoparticles have different inclinations over microparticles (>1 μm) as a pharmaceutical movement structure (Otto et al. 2015). Nanoparticles have another great position over greater microparticles in light of the fact that they are more fit the bill for intravenous transport (Pathak and Thassu 2016). The humblest vessels in the body are 5–6 μm in width. The traverse of particles being circled into the circulatory framework must be on a very basic level humbler than 5 μm, without surrounding aggregates, to ensure that the particles do not cause an embolism.

The use of biodegradable materials for nanoparticle availability considers kept up pharmaceutical release inside the target site over a period of days or even weeks (Elzoghby et al. 2018; Li and Lim 2018). Biodegradable nanoparticles point by point/figured from PLGA and PLA have been created for the managed sedate conveyance which bolstered solution movement and are especially effective for drugs with an intracellular target (Barrera et al. 1993; Bee et al. 2018; Chereddy et al. 2018; Davda and Labhasetwar 2002).

18.5 Demerits in Nanoparticle Development

Nanotechnology is a multidisciplinary scientific field with notable advantages along with some disadvantages. There are many difficulties that emerge in the early- and late-stage advancement of therapeutic nanoparticles that are either nonexistent or insignificant in non-nanoparticle-based treatments. The essential driver of these issues is the progressive and non-uniform nature of nanoparticles, which implies that a little change in a solitary property can effectively affect the pharmacokinetics or remedial viability of the molecule. For instance, one basic issue is keeping up a tight dispersion of molecule estimate. For most applications, a molecule estimate under 200 nm is attractive. With an expansive typical appropriation of sizes, this implies regularly the normal molecule must be too little to be in any way valuable keeping in mind the end goal to restrict the quantity of particles more than 200 nm. It is therefore alluring to have an assembling procedure that guarantees tight size dispersion (Desai 2012).

Moreover, numerous one of kind difficulties can emerge amid the trial and creation phases of the nanoparticle. As a rule, a strategy for nanoparticle development that is appropriate in a laboratory setting is inappropriate in an industrial facility, and the union advances must be totally revamped. In a production line, the variety in nanoparticle structure must be littler, the yield must be higher, and the combination must be more sterile than what is satisfactory in a laboratory. These things can make a molecule unviable to deliver regardless of the possibility that it works. In the event that a molecule is sold, it must be rack stable, which implies that it both won't corrupt in the arrangement and that it won't cluster after some time, as nanoparticles frequently do. At last, nanoparticles confront additional administrative difficulties as their danger is substantially harder to decide than that of a little atom. This extraordinarily expands the duration and cost of clinical trials. These difficulties consolidated imply that it is constantly reasonable to consider inquiries of adaptability and reproducibility even at the most punctual phases of advancement to anticipate disappointment at a later stage (Xing et al. 2016).

18.6 Examples of Nanocarriers

18.6.1 Dendrimer Nanocarriers

Dendrimers are another class of polymeric materials. A dendrimer is ordinarily symmetrical around the center and regularly embraces around three-dimensional engineering that gives a high level of surface usefulness and adaptability. Different uses of dendrimers have been investigated amid the most recent three decades. Their synthesis procedure includes repetitive alteration of growth and activation reactions at many locales of the same molecule to provide large binding sites for drug binding. Commonly Michael reaction, or the Williamson ether synthesis, solid-phase synthesis, organotransition metal chemistry, organophosphorous chemistry, and organosilicon chemistry are chosen to get highly branched dendrimer as the product (Karanjavkar et al. 2016). On the basis of functional and structural units, dendrimers are classified into polyamidoamine dendrimers (PAMAM), polyamidoamine-organosilicon dendrimers (PAMAMOS), poly (propylene imine) (PPI) dendrimers, micelles, and hybrid dendrimers (Karanjavkar et al. 2016; Verma et al. 2015). Advancement in controlled polymerization and amalgamation strategies have prompted the rise of all around controlled dendrimers structures with a substantial number of surface gatherings that can be used to show a scope of organic particles including peptides, proteins, sugars, and targeting particles (Huang and Wu 2018; Vaidya et al. 2018). The monodispersity, polyvalency, biocompatibility, small structure, and elemental properties of dendrimers make them very valuable in the medical field (Karanjavkar et al. 2016; Verma et al. 2015). The high stacking limit of dendrimers also renders them very alluring as transporters for the conveyance of chemotherapeutic specialists. PEGylated and non-PEGylated dendrimers demonstrated to embody hydrophobic sedate particles into the empty voids of their spreading design, which upgrade the fluid dissolvability and security of the embodied medication particles (Luong et al. 2016; Sharma et al. 2017). Both targeted and non-targeted dendrimer medication edifices effectively infiltrate over the tumor's broken vasculature and aggregate in the malignancy tissue (Kesharwani and Iyer 2015; Luong et al. 2016). Directed dendrimer-tranquilized buildings have the added favorable position of specifically official to the receptors shown on the surface of growth cells, which builds their living arrangement time on the cell surface and upgrades their disguise energy into the cell (Tripathy and Das 2013).

Previously, dendrimer-based drug transportation systems were based on the encapsulation of drugs. They are characterized as exceptionally ordered and consistently expanded globular macromolecules delivered by stepwise iterative methodologies. However, the release of drug with dendrimers is difficult to control. The structure of dendrimers comprises of three particular building blocks: a central moiety or a center, layers of bifurcated iterative units rising up out of the center, and functional end moieties on the external layer of iterative units (Ahmed et al. 2016; Kaur et al. 2017). The existence of a few surface functional moieties empowers a synchronous cooperation with various receptors, and along these lines, it upgrades organic action (Caminade et al. 2015; Hu et al. 2016). The medication might be epitomized in the inside structure of dendrimers or it can be synthetically appended or physically adsorbed on dendrimers surface (Kesharwani et al. 2014).

A number of studies have been conducted on the use of dendrimers nanocarriers in animal models of diseases, specifically, cancer or pulmonary disease models. In recent years, several anticancer drugs have been studied in tumor treatment associated with functionalized dendrimers. Zhang et al. have developed enzyme-responsive PEGylated lysine peptide dendrimer-gemcitabine conjugate (Dendrimer-GEM) and studied their antitumor efficiency in 4T1 murine breast cancer model with significant tumor inhibition and no toxic effect (Zhang et al. 2017). The high penetration power of poly(amidoamine) have made a remarkable position in dendrimer-based drug delivery, but their cytotoxicity due to positive charge and rapid clearance in in vivo systems can be minimized via dendrimer functionalization. In this direction, Qi and colleagues have demonstrated doxorubicin-loaded carboxymethyl chitosan-modified polyamidoamine dendrimer for targeted drug delivery in H22 tumor model of mice, and significant results in pH-sensitive-based antitumor activity were reported (Qi et al. 2016). Similarly, fluorouracil conjugated PAMAM/5 (PAMAM/5-FU) was reported to target E6/E7 oncoproteins in cervical cancer model of BALB/c female mice (Rengaraj et al. 2017). They also performed in silico experiments on COS-7 and HeLa cell lines to demonstrate PAMAM/5-FU and E6/E7 oncoproteins interaction and lower toxicity of dendrimers. In another study, PAMAM G3 dendritic microsphere was used for rifampicin delivery to lung tissues, and significant results in drug adsorption at lower toxicity were observed in tuberculosis animal model

(Rajabnezhad et al. 2016). In another study, doxorubicin (Dox) conjugated PEGylated (PEG570) G4 polylysine dendrimers have also reported affective results in intravenous and pulmonary pharmacokinetics of rats (Leong et al. 2018). In a similar study, Mehta and colleagues have also reported PEGylated G5 dendrimer associated cathepsin-mediated doxorubicin release in rodents, in which use of 570 versus 1100 Da PEG completely avoid enzyme restriction to access peptide-based drug linkers and improve targeted drug delivery (Mehta et al. 2018).

Recently, several other studies have been focused on the advanced version of smart dendrimeric delivery. Li and colleagues have developed docetaxel (DTX) loaded hyaluronic acid (HA), poly(lactide) (PLA) and poly(amidoamine) dendrimers (sPA G4.5) conjugated nanocarrier in enhanced anticancer activity in in vivo system (Du et al. 2018). Lin et al. have also developed dendrimer-dexamethasone (D-Dex) for therapeutic use in a rabbit model of induced autoimmune dacryoadenitis (AID) through single subconjunctival injection, and significant results in pathology-dependent biodistribution were observed (Lin et al. 2018a). In another studies, dendrimer based drug delivery was used in animal models of neural diseases. In this direction, Gothwal and colleagues have designed rivastigmine (RIV) loaded lactoferrin (Lf) conjugated polyamidoamine generation 3.0 (PAMAM G3.0) dendrimers for Alzheimer's animal model (Gothwal et al. 2018). The pharmacokinetics study demonstrated low hemetoxicity and improved bioavailability of modified drug improved delivery to site specific targeting. In another study, PEGylated fifth-generation polyamidoamine dendrimer (mPEG-PAMAM) conjugated Arg-Gly-Asp (RGDyC) and αvβ3 integrin targeting ligand for targeting delivery to glioma cells in in vivo study (Lu et al. 2018b). The low cytotoxicity, improved targeted drug delivery, and anticancer activity were significantly reported in the study. In a similar direction, carbamazepine (CBZ) associated ethylenediamine core, generation 4.0 (amine terminal groups) and 4.5 (carboxylate terminal groups) (DG4.0 and DG4.5, respectively) based PAMAM dendrimer based drug delivery in a zebrafish model of Alzheimer's disease (Igartúa et al. 2018).

Not restricted to this drug delivery, dendrimers also reported in gene or protein delivery in therapeutics. Malkoch and colleagues reported cationic amino group functionalized dendrimers associated 2,2-bis(methylol)propionic acid (bis-MPA) conjugated siRNA delivery in brain tumor cells (Stenström et al. 2018). In this novel study, researchers used fluorescent tagged siRNA loaded dendrimers and examined endocytotic pathway delivery which results in reduced p42-MAPK expression in C6 and U87 cell lines. Similarly, siRNA loaded polyamidoamine dendrimers grafted halloysite nanotubes (PAMAM-g-HNTs) were reported for intracellular gene delivery in cancer cell lines (Long et al. 2018). In another study, reactive oxygen species (ROS)-responsive dendrimer poly(amidoamine)-*N*-(4-boronobenzyl)-*N*,*N*-diethyl-2-(propionyloxy)ethan-1-aminium (PAMAM-(B-DEAEP)$_{16}$), an zwitterionic dendrimer, have reported in efficient gene delivery with low toxicity and improved site specific transfection (Li et al. 2019). In continuation of this, Lin and colleagues reported gemcitabine (Gem) and miR-21 inhibitor (miR-21i) conjugated dendrimer-entrapped gold nanoparticles (Au DENPs) in pancreatic cancer (PaCa) in in vivo and in vitro tumor cells (Lin et al. 2018b). This was the first study to be reported in co-delivery of drug-gene conjugated transport for therapeutic purpose.

After some up and down in nanocarrier use in medicine, U.S. Food and Drug Administration (FDA) allowed the clinical trials of dendrimer-based VivaGel™ for vaginal infection in July 2003 (McCarthy et al. 2005; Rupp et al. 2007). The field of dendrimers in medicine is increasing in all these years, for examples, Dade Behring manufactured StratusTMCS used as cardiac biomarker (Singh 2007), Qiagen announced SuperFect for gene transfection, and gold standard of US Army Research Laboratory in Alert Ticket™ for anthrax detection (Shah and Singhvi 2014). Other than this, Avidimer Therapeutics, Ann Arbor, MI developed Avidimers™ and Starpharma developed docetaxel (Taxotere) program for effective anticancer activity in the clinical market (Shah and Singhvi 2014). Similarly, collaborative work of Starpharma and Dendritic Nanotechnologies (Mount Pleasant, MI) results into development of Priostar™, a dendrimer-based NanoJuice transfection kit (Shah and Singhvi 2014; Tolia and Choi 2008).

18.6.2 Carbon Nanomaterials

Carbon nanomaterials utilized as a part of delivery frameworks which are separated into nanotubes (CNTs) and nanohorns (CNH), are used vastly, in variety of fields owing with its specific size associated functions and physiochemical properties (Chandrasekhar 2018; Karousis et al. 2016; Mehra et al. 2015). On the basis of their prototypic structure and shape, CNT are classified into single-wall carbon nanotubes (SWNT), multiwall carbon nanotubes (MWNT), double-walled carbon nanotube (DWCNT), carbon nanohorns, carbon nanobud, and carbon nanotorus (Beg et al. 2011). After advancement in nanomaterial synthesis, the CNT is basically synthesized from electric arc discharge (EAD), catalytic chemical vapor deposition (CVD), laser ablation technique (LA), plasma-enhanced chemical vapor deposition (PE-CVD), and high-pressure carbon monoxide disproportionation process (HiPCO) techniques which can be characterized through SEM, TEM, AFM thermogravimetric analysis (TGA), infrared spectroscopy (IR), nuclear magnetic resonance (NMR), and Raman spectroscopy (Beg et al. 2011). Nanotubes (CNTs) are portrayed by remarkable design shaped by moving of single-walled CNTs or multiwalled CNTs layers of graphite with a huge surface region and an amazing thermal and electronic conductivity (Ahmed et al. 2018; Karimi et al. 2015). The effortless penetration to the plasma membrane and high loading capacity of CNTs make them unique in medical diagnosis and new therapeutic intervention (Zhang et al. 2010). Still, poor dispersibility of CNT calls for covalent and non-covalent functionalization to improve biocompatibility and solubility of carbon nanomaterials in a biological system (Lee et al. 2008; Meher et al. 2018; Zhang et al. 2010). Other than this, amorphous carbon and metallic nanoparticle-based impurities on CNT can also be removed through surface functionalization with carboxylic acid that can be further converted into acid chloride or cycloadditions and improved elemental and physiochemical properties of CNT (Prato et al. 2007). Medication discharge from CNTs can be electrically or synthetically controlled. To keep the undesirable arrival of the medication, the open finishes of CNTs were fixed with. Nanohorns are single-divider nanotubes which do not require a metal impetus for the definition, and along these lines, they can be effectively arranged with ease and are of high immaculateness (Zhang et al. 2015). Although, there are the excellent advancement in CNT development and their use in drug delivery and diagnostics, still the toxicity level are always main concern for CNT use. Other than toxicity, the different CNT replication in different batches or different manufacturer also limits the CNT use in core medical field. Therefore, unlike other nanocarriers, CNT did not achieve such commercial success, although more studies have been reported in CNT-based nanocarrier in imaging instead of drug therapy.

Recently, Chlorin e6 (Ce6), albumin coupled fluorescent photosensitizer, decorated SWCNT, were used in imaging and photodynamic therapy in tumor imaging, in which Evans blue conjugated nanotubes helped in the enhancement of in vivo stability and circulation time (Xie et al. 2016). This study also focused on SWCNT-based dual theranostic system in both synergistic photodynamic therapy (PDT) and photothermal therapy (PTT) for cancer treatment. In another study, paclitaxel and salinomycin loaded CD44 antibody SWCNTs conjugated nanocarrier system were not only reported noninvasive bioluminescence imaging, but they also demonstrated effective treatment of breast cancer (Xie et al. 2016). Similarly, doxorubicin associated transactivator of transcription (TAT)-chitosan functionalized MWCNTs (MWCNTs-TC) was synthesized, and significant results in targeted drug release and antitumor activity along with noninvasive fluorescence and luminescence imaging were observed in cancer treatment therapy (Dong et al. 2017b). Dong and colleagues also demonstrated IR light-induced doxorubicin delivery through chitosan decorated multiwalled carbon nanotubes (MWCNTs) through the photothermal effect of CNT in drug release as well as real-time fluorescence imaging in nude mice model (Dong et al. 2017a).

Due to the toxicity of CNTs, researchers are using biomolecule functionalized CNTs in targeted drug delivery, mostly folic acid decorated nanotubes. Kayat and colleagues have designed anti-arthritic drug, methotrexate (MTX), loaded folic acid linked MWCNT nanocarrier in arthritis treatment in in vivo and in vitro system and proved sustained and targeted drug delivery (Kayat et al. 2016). Similarly, doxorubicin/coumarin-6 loaded chitosan-folate conjugated MWCNT were also demonstrated significant targeted drug delivery and low cytotoxicity in lung cancer cells (Singh et al. 2017). In direction of improved biocompatibility in CNT-based drug delivery, Harrison and colleagues have developed annexin V (AV) and phosphatidylserine decorated SWCNT, and significant antitumor activity in orthotopic MB49 murine bladder tumor in mice in the presence of near-infrared (NIR) light was observed (Virani et al. 2017). In another study, PEGylated CNTs were reported in chondrocyte-rich cartilage, meniscus and synovial membrane regions targeted delivery in mice animal model (Bhattacharya et al. 2018). They mainly focused on nitric acid-induced PEG degradation in site-specific delivery and reported their efficiency. Behnam et al. have developed plasmonic photothermal therapy (PPTT)-based therapeutic treatment for melanoma tumor (Behnam et al. 2018). They developed silver nanoparticles conjugated CNTs and studied improved tumor destruction in inbred mice model of solid tumor.

High penetrability of CNTs was also reported in several researches in the animal model of CNS disorders. Li and colleagues reported lactoferrin-nanoparticle (Lf-NP) conjugated PEGylated SWCNTs in treatment of Parkinson's disorder (PD) in OHDA-lesioned mice model of PD and significant reduction of oxidative stress and inflammatory response along with increased tyrosine hydroxylase-immunoreactive (TH-ir) density observed in the striatum of PD mice model (Guo et al. 2017). Similarly, recombinant human erythropoietin-loaded chitosan nanoparticles (rhEpo-CNPs) decorated polylactic acid (PLA), MWCNTs, and gelatin nanofibrils (GNFs) nanocarrier system were developed for schwann cells induced sciatic nerve regeneration in Wistar rats (Salehi et al. 2018). In continuation of brain cell-targeted delivery, Chen and colleagues have recently made an effort in oxaliplatin-associated-MWCNT-based nanocarrier for orthotopic glioma therapy and opened new gateway for nanodrugs development (You et al. 2019).

Other than conventional CNT based drug delivery platform, recent studies have focused on aptamers and molecularly imprinted polymer (MIP) supported nanocarriers for site-specific delivery system. Zhang and colleagues have designed levofloxacin (LVF)-based MWCNT associated MIP which was reported improved bioavailability and controlled drug release in in vivo (Zhang et al. 2018). Similarly, SWCNT associated fenbufen (FB)-based MIP reported superior controlled release with low toxicity in male Wistar rats (Liu et al. 2018). In another study, PEG and anti-PSMA aptamer conjugated MWCNTs was introduced as advanced ultrasound contrast agent for prostate cancer (PCa) prognostic which results into excellent cell uptake and biocompatibility of contrast agent in male BALB/c nude mice (Gu et al. 2018).

The several patented carbon-based nanomaterials are already in work-in-progress. The Ensysce Biosciences Inc. has received approval for the clinical trial on SWNT-based siRNA delivery for cancer treatment (Lewinski 2005). The collaborative efforts of Tego BioSciences Corporation (Tego) and Bronx Project, Inc. (TBP) also initiated clinical trial on patented carboxylated fullerenes (C3) in Parkinson's disease, schizophrenia, amyotrophic lateral sclerosis (ALS), brain trauma, and multiple sclerosis treatment (http://www.nanowerk.com/news/newsid=16674.php). Similarly, Carbon Nanotechnologies, Houston, TX, USA, and Merck & Co, Inc. (Whitehouse Station, NJ, USA) have received a license to develop antioxidant fullerene-based therapeutics in 2003 (Wagner et al. 2006). Still cytotoxicity and genotoxicity of CNT based drug delivery system oculate their use in medicine and no well-defined product available in the market. Not limited to these, several other industries like MagForce Nanotechnologies AG, Philips Research NV, Liquids Research Ltd, Micromod GmbH, Bayer Schering Pharma, Midatech Ltd., NanoPET GmbH, Promethean Particles Ltd., and Pepric NV have established a model via developing magnetic nanoparticle-based contrast agents in healthcare (Pankhurst et al. 2003). Bayer Healthcare Pharmaceuticals is under phase II of a clinical trial for carboxy-dextran coated USPIO magnetic component, marketed as Ferucarbotran/Supravist® and GE healthcare is under phase III clinical trial for starch/PEG-coated FeruglosePEG-feron/Clariscan® USPIO for MRA, lymph nodes, liver, spleen alteration (Ittrich et al. 2013). GE Healthcare and AMAG Pharmaceuticals Guerbet have also developed silicon and styrol/ divinylbenzene coated SPIOs marketed in name of Ferumoxil/ GastroMARK®, Lumirem® and Ferristene/Abdoscan® for gastrointestinal diseases (Ittrich et al. 2013).

18.6.3 Magnetic Nanoparticles (MNPs)

Magnetic nanoparticles can be controlled using magnetic field commonly consists of magnetic elements such as Fe, Ni, Co, and their compound ranging 1–100 nm (Soni et al. 2016). Among several methods, co-precipitation, sonochemical, chemical vapor deposition carbon arc, microemulsion, and microwave-assisted MNPs synthesis techniques are most common and feasible in the laboratory (Akbarzadeh et al. 2012; Cardoso et al. 2018). The magnetic nanoparticles need to have a wide range of magnetism recording, high stability, flexible to different magnetic states and not affected by temperature fluctuations during their use in biomedicine, though supermagnetic nanoparticles preferred (Akbarzadeh et al. 2012). Other than this, these NPs are simple handling with the guide of an outer attractive field, the likelihood of utilizing uninvolved and dynamic medication conveyance methodologies, the capacity of representation, and upgraded take-up by the objective tissue bringing about successful treatment at the remedially ideal measurements (Inozemtseva et al. 2018; Kudr et al. 2017; Reiss and Hütten 2016). The in vivo administration of MNPs requires biocompatible polymers coating to avoid the toxic effect, NP aggregation, structural change, and easy biodegradation (Akbarzadeh et al. 2012). Commonly, magnetite (Fe_3O_4) or its oxidized form maghemite (g-Fe_2O_3) is used in biomedical applications, unlike cobalt and nickel as they are vulnerable to oxidation and exhibit toxicity (Johnston-Peck et al. 2018).

Magnetic nanoparticle-based drug delivery and imaging techniques work on magnetic field stimulated transport and mostly iron and d-block metallic nanoparticles used in these aspects. In direction of complete destruction of tumor cells, Hilger and colleagues have designed Nucant multivalent pseudopeptide (N6L; MF66-N6L), doxorubicin (DOX; MF66-DOX) functionalized superparamagnetic iron oxide nanoparticles (MF66) and demonstrated reduced tumor growth and proliferative activity in female athymic nude mice model of breast cancer (Kossatz et al. 2015). Similarly, doxorubicin (Dox)-conjugated heparin (DH-SPIO) decorated superparamagnetic iron oxide (SPIO) nanoparticles (NPs) also reported as dual-mode activity mode as both drug delivery carrier and imaging contrast (Yang et al. 2016). In another study, biopolymer poly(lactic-co-glycolic acid) functionalized Fe_3O_4 was not only reported with improved drug payload, but it also provided upgraded fluorescence imaging of tumor tissues (Park et al. 2016). The brain-related diseases also in touch with magnetic nanoparticles based on therapeutic and diagnostic use. One study completely focused on paclitaxel and curcumin based combinational drug delivery which is decorated transferrin receptor-binding peptide T7-modified magnetic PLGA nanoparticle in treatment of glioma cells in rats (Cui et al. 2016). They demonstrated dual targeting of transferring and PLGA-modified nanocarrier in improved therapeutistics. Xu et al. reported doxorubicin-loaded superparamagnetic iron oxide core and PEG/PEI/polysorbate 80 (Ps 80) based multifunctional shell nanocarrier system in both imaging and drug delivery purpose in rat model of glioma (Xu et al. 2016). They studied cytotoxicity, magnetic field-induced drug delivery, and real-time imaging of DOX loaded multifunctionalized polymeric magnetic nanocarriers along with the mechanism of action in cancer cells (apoptosis through the caspase-3 pathway). Similar study was conducted with the use of DOX-loaded PEGylated superparamagnetic iron oxide nanoparticles that accumulated on solid tumor cells to help in improved resolution of imaging (Liang et al. 2016). This research also demonstrated crosslinking between DNA and SPIO-PEG-D nanocarrier that lowered the cell division and hence stopped cancer cell growth. In another study, Depireux and team have synthesized prednisolone loaded iron oxide nanoparticles for target specific transport into cochlea for improved ear histopathology in rats (Lafond et al. 2018).

In the direction of photodynamic therapy, modified magnetic nanomaterials have played a significant role. Liu and colleagues have developed DOX-loaded PEGylated mesoporous silica shell decorated WS_2 nanosheets and iron oxide nanoparticles assembly in NIR photothermally induced killing of cancer cells (Yang et al. 2015). They demonstrated the synergistic therapeutic effect of upgraded 2D nanocomposites in combined chemotherapy and imaging therognostic. Similarly, methotrexate (MTX) loaded arginine-glycine-aspartic acid (RGD) conjugated PEGylated gold (Au)/iron (Fe)/gold (Au) shelled nanoparticles were used in NIR stimulated magnetic targeted chemo-photothermal treatment along with multimodal imaging of rheumatoid arthritis (RA) in mice (Kim et al. 2015). This combined NIR irradiation and external magnetic field application significantly improved the therapeutic effect of MTX. Recent study on photosensitizer protoporphyrin IX (PpIX)-loaded superparamagnetic iron oxide nanoparticles (SPIONs) not only showed advanced magnetism, but they also reported with high loading and potent characteristics to reduce tumor cell growth rate in a syngeneic murine tumor model during photodynamic therapy (Yan et al. 2018). Another study focused on mesoporous bioglass (BG)/chitosan (CS) porous scaffold (MBCS) modified magnetic $SrFe_{12}O_{19}$ nanoparticles in treatment of BMP-2/Smad/Runx2 pathway-based bone regeneration under irradiation of NIR lights (Lu et al. 2018a).

Several studies have been conducted in direction of the use of hybrid magnetic nanoparticles in imaging as well as therapeutics. Recently, Nigam and Bahadur have assessed DOX loaded dendrimeric Fe_3O_4 nanoparticles in C57BL/6 mice model of spheroid melanoma (Nigam and Bahadur 2018). They reported elevated tumor and drug localization in rats, which significantly enhanced imaging as well as drug delivery. In another study, DOX-loaded MMP-2 enzyme responsive peptide conjugately bounded with mesoporous silica-coated iron oxide nanoparticles

(Fe_3O_4@MSNs) and use them as MRI contrast agent as well as controllable drug released nanocarrier to inhibit tumor cell growth (Li et al. 2018a).

To keep clinical prospective of MNPs in healthcare, the impact of particle size on distribution, kinetics and dynamics of drug or contrast conjugated MNPs, their drug release mechanism and their effect on cellular physiology need to be taken care of, although their circulation time and clearance from the body are an extended limitation (El-Boubbou 2018). The first effort to use of epirubicin-loaded magnetic nanoparticles in a clinical trial in cancer therapy was led by Dr. Lübbe in 1996, but 50% of the drug was ended up accumulating in liver (Lübbe et al. 1996). Since then, several groups have demonstrated the application of magnetic nanoparticles in diagnostics as well as in therapeutic intervention. In this direction, FeRx, Inc has started a phase II clinical trial for metallic Fe and activated carbon encapsulated doxorubicin in primary liver cancer patients, although the trail was completely failure (Goodwin et al. 1999, 2001). In continuation of these, Chemicell GmbH has commercialized multidomain magnetite core conjugated starch matrix with terminal cations based TargetMAG-doxorubicin in cancer therapy (Steinfeld et al. 2006). They also marketed fluidMAG® for drug delivery. Similarly, Alnis BioSciences, Inc. has also developed chemotherapeutic agents, Fe oxide colloids, and targeting ligand-based magnetic NP hydro-gel (MagNaGel®) in cancer treatment (Sunderland et al. 2006). In continuation of this, Schering (Berlin) and Advanced Magnetics (Cambridge, MA, USA), Guerbet (Roissy, France) have developed iron NP-based contrast agents, Resovist® and Feridex/Endorem®, respectively, for liver tumor in vitro imaging, though Advanced Magnetics, Guerbet developed iron NP-based Gastromark/Lumirem® and reported in abdominal structural imaging (Wagner et al. 2006). Dynal/Invitrogen (Oslo, Norway), Miltenyi Biotec (Bergisch Gladbach, Germany), and Immunicon (Huntingdon Valley, PA, USA) also designed magnetic NP-based immunodiagnostics in clinical cell separation (Wagner et al. 2006). Several other superparamagnetic iron oxide nanoparticles (SPION) are also in clinical phases, some of them are as follows: Dextran-coated approved contrast agents Ferumoxytol (AMI-121)/Lumirem® (Guerbet), Gastromark® (Advanced Magnetics); Ferumoxide (AMI-25, SHU 555A)/Endorem® (Guerbet), Feridex® (Advanced Magnetics); Ferrixan® (Ferucarbotran, SHU 555A)/Resovist® (Schering), Cliavist® (Medicadoc); Ferumoxtran-10 (AMI-227, BMS-180549)/ Sinerem® (Guerbet), Combidex® (Advanced Magnetics) and sulfonated styrene–divinylbenzene copolymer coated Ferristene (OMP)/Abdoscan® (GE-Healthcare), unlikely carbohydrate–PEG coating (PEGylated starch) in Feruglose (PEG-feron, NC100150)/Clariscan (GE-Healthcare) which was discontinued from the market (El-Boubbou 2018; Reddy et al. 2012). Further advancement in the directed application of magnetic nanoparticles were reported in sentinel lymph node detection (Endomagnetics Ltd., UK), gene transfection (NanoTherics Ltd., UK), magnetic hyperthermia (Aduro Biotech Inc., USA and Sirtex Medical Ltd., USA) and magnetic immunoassays (MagnaBioSciences LLC., USA) (Pankhurst et al. 2003). After some hurdles and adverse events of Resovist®, Endorem®, Sinerem®, and Combidex®, they were withdrawn from market and ferumoxytol was investigated due to pancreatic inflammation (Tietze et al. 2015). Instead of the unique properties of magnetic nanoparticles, it still needs further advancement to be used in clinical applications.

18.6.4 Polymeric Nanoparticles (PNPs)

PNPs are solid colloidal particles ranging in size from 10 to 100 nm (Soni et al. 2016). These are produced using an assortment of regular and engineered polymers which are considered, as the most encouraging medication transporter. PNPs are basically steady and can be orchestrated with a keener size conveyance. Polymeric-based nanoparticles effectively carry drugs, proteins, and DNA to target cells and organs (Couvreur et al. 2018; Kamaly et al. 2016). Their nanometer size promotes effective permeation through cell membranes and stability in the bloodstream (Lim et al. 2018; Reis et al. 2017). The surface of PNPs contains useful moieties that can be synthetically altered with either sedate moieties or focusing on ligands delivery. PNPs are typically covered with non-ionic surfactants keeping in mind the end goal to lessen immunological cooperation and in addition intermolecular communications between the surface chemical moieties of PNPs (Bennet and Kim 2014).

Polymer-based drug delivery is the second most common method for effective and safe drug delivery as well as imaging. Cui and colleagues have developed colon targeted icariin-loaded alginate-chitosan microspheres in the treatment of ulcerative colitis and lowering inflammatory response was reported rats (Wang et al. 2016).

The adverse reactions of anticancer drugs are predominantly avoided by use of polymeric nanoparticle-based targeted drug delivery. Chen and colleagues have designed cisplatin crosslinked DOX-loaded polysaccharide-based nanoparticles (Dex-SA-DOX-CDDP) which demonstrated anticancer activity and sustained drug release in in vivo model of colorectal carcinoma, dimethylhydrazine-induced autochthonous colorectal carcinoma, and metastatic mammary carcinoma (Li et al. 2015). In direction of cancer treatment, Chen et al. have developed docetaxel (DTX) loaded aptamer-anchored functional PLGA-b-PEG and sodium oleate functionalized polymeric nanoparticles (apt-NPs) and reported adequate drug distribution along with effective antitumor activity in in vivo prostate cancer animal model (Chen et al. 2016).

In direction of neural treatment, several studies have been conducted on polymeric nanocarrier-based targeted drug or nucleotide delivery. In a study of glioma treatment, angiopep-2 functionalized DOX loaded PEGylated AuNP reported pH-sensitive sustained drug release in glioma bearing mice (Ruan et al. 2015). Similarly, FITC-albumin-loaded 7-aminoacid glycopeptide (g7) functionalized PLGA NP was reported to correct pathological phenotype of neurological impairment associated murine models for lysosomal storage disorder (Salvalaio et al. 2016). In another study neuropeptide Substance P (SP) loaded gelatin NP was reported in the treatment of 6-hydroxydopamine (6-OHDA)-induced hemiparkinsonian rats and resulted into reduced dopaminergic neuron apoptosis (Zhao et al. 2016). Recent studies not only focused on drug delivery to brain, but they also reported siRNA or protein transport to the brain. In this direction, Carradori et al. have reported the use of PEGylated $A\beta_{1\text{-}42}$ antibody-loaded polymeric nanoparticles in the treatment of AD and effectively recover the memory in a rodent model of

AD (Carradori et al. 2018). Similarly, poly(lactide-co-glycolide)-graft-polyethylenimine (PgP)-based polymeric micelle NP encapsulated nucleic acid and rolipram (Rm), a phosphodiesterase IV inhibitor, demonstrated efficient reduced secondary neural injury along with reduced inflammation and neural apoptosis in in vivo model of SCI (Macks et al. 2018).

Not restricted to these, PNP nanocarrier efficiently approved in insulin based targeted delivery. Previously, insulin-loaded polyethylene imine-based nanocarriers demonstrated effective controlled release in diabetic rats (Salvioni et al. 2016). Similarly, Pham et al. demonstrated immunosuppressant FK506-loaded 3,4–dihydroxyphenethylamine (DOPA) conjugated poly(lactide-co-glycolide)–poly(ethylene glycol) (PLGA–PEG) nanoparticles (DOPA-NPs) as an effective treatment therapy in diabetic mouse model (Pham et al. 2018). In another study of insulin transport, researchers used PEG, poly(phenylboronic acid) (glucose-sensitive block), and poly(phenylboronic acid pinacol ester) (H_2O_2-sensitive block) in diabetic rats (Tong et al. 2018).

The polymer-based nanocarriers have made significant progress in pharmaceuticals and medical sciences. Most commonly PEG conjugated drug is basically used in medicals, some of them are: PEG–adenosine deaminase conjugated Adagen® by Enzon, was reported in severe combined immunodeficiency disease associated with ADA deficiency treatment, PEG-anti-VEGF aptamer conjugated Macugen® by OSI Pharmaceuticals (Melville, NY, USA) and Pfizer (New York) in age-related macular degeneration therapy, PEG-a-interferon-2a-based Pegasys® by Nektar (San Carlos, CA, USA), Hoffmann-La Roche (Basel) in Hepatitis B and C treatment, PEG–GCSF associated Neulasta® by Amgen (Thousand Oaks, CA, USA) in neutropenia associated with cancer chemotherapy, PEG–HGF named as Somavert® by Nektar, Pfizer for acromegaly treatment and PEG–L-asparaginase conjugated Oncaspar® by Enzon for Acute lymphoblastic leukemia therapy (Bamrungsap et al. 2012; Wagner et al. 2006; Zhang et al. 2008). Similarly, TEVA Pharmaceuticals (Petach Tikva, Israel) and Genzyme have individually developed copolymer of alanine, lysine, glutamic acid, and tyrosine, marketed in name of Copaxone® and poly(allylamine hydrochloride)-based Renagel® for multiple sclerosis treatment and end-stage renal disease, respectively (Bamrungsap et al. 2012). In another study, Samyang has marketed methoxy-PEG-poly(D,L-lactide) taxol with brand name Genexol-PM® for the treatment of metastatic breast cancer (Zhang et al. 2008). In continuation of all these, various other polymeric-drug conjugates are in clinical trials and reported to be more beneficial in treatment therapies. The doxorubicin and paclitaxel-loaded PEG-based PEG-PAA-DOX, named NK911 and PEG-PLA-Taxol, named Genexol-PM, respectively, are in clinical trial (Prakash et al. 2011). PEG conjugated anti-TNF-α antibody fragment, named Cimzia by Nektar, -arginine deaminase, named Hepacid by Phoenix, -naloxol, named NKTR-118 by Nektar, -uricase, named Puricase by Phoenix and -camptothecin, named Prothecan by Enzon are under clinical trials for treatment of rheumatoid arthritis and Crohn’s disease, hepatocellular carcinoma, opioid-induced constipation, hyperuricemia from gout and several other cancers, respectively (Zhang et al. 2008). Poly-L-glutamic acid (PGA) coated camptothecin based polyglutamate-camptothecin, named CT-2106 for colorectal and ovarian cancer and paclitaxel, named polyglutamate-paclitaxel CT-2103, Xyotax™, OPAXIO™ were also showing significant results in ovarian and lung cancer treatment (Prakash et al. 2011; Zhang et al. 2008). Both have successfully crossed phase II clinical trial (https://clinicaltrials.gov). Some other clinical trials are under progress for the use of *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymer conjugated with doxorubicin, carboplatin palatinate, DACH palatinate and doxorubicin galactosamine named PK1and FCE28068, AP5280, AP5346/ProLindac™, and PK2/FCE28069, respectively, for cancer therapy (Prakash et al. 2011). BioAlliance Pharma also has under process clinical trial for doxorubicin conjugated poly(iso-hexyl-cyanoacrylate), named Transdrug for hepatocellular carcinoma (Zhang et al. 2008). Till now, none of them are withdrawn from clinical trials and reported in moving forward in soon-to-be marketed categories.

18.6.5 Lipid Nanoparticles

SLNs (solid lipid nanoparticles), NLCs (nanostructured lipid transporters), and LDC (lipid drug conjugates) are new therapeutic which help to control drug release (Sala et al. 2018; Sánchez-López et al. 2017). These are sorts of carrier frameworks in view of the lipid matrix, which imparts strength (Beloqui et al. 2016; Sala et al. 2018).

Solid lipid nanoparticles or SLNs are particles or new generation of submicron size lipid emulsion which is made of strong lipids, for example, triglyceride, complex glyceride blends, or waxes balanced out by different surfactants (Garcês et al. 2018; Geszke-Moritz and Moritz 2016; Yagoubi et al. 2018). The principle attributes of SLNs incorporate decent physical dependability, assurance of fused medications from destruction, controlled medication discharge, and great tolerance capacity (Kakkar Thukral et al. 2014; Yagoubi et al. 2018). SLN proved themselves improved version of emulsions, micelles, liposomes, and polymeric NPs in terms of biocompatibility, although they still have low drug loading capacity due to crystalline structure and lipid aggregation (Dolatabadi and Omidi 2016). Compritol®888 ATO, stearic acid, Precirol® ATO5, cetylpalmitate, glyceryl monostearate, cetyl alcohol, trimyristin/Dynasan®114, tristearin/Dynasan®118, and Imwitor®900 are the most common lipids used in SLN synthesis without the use of any toxic chemicals (Dolatabadi and Omidi 2016). Nanostructured lipid transporters or NLCs are adjustments of SLN and it is called as a second era of lipid nanoparticles. NLCs are created by blending strong lipids with fluid lipids, which prompts unique nanostructure with expanded payload and forestalled drug ejection (Beloqui et al. 2016; Garcês et al. 2018) It is basically a mixture of solid, semi-solid/liquid lipids and aqueous phase of surfactant with resultant structure in nanorange (Fang et al. 2008). Basically, microemulsification, solvent displacement, and high-pressure homogenization process are used in NLC production (Beloqui et al. 2016). Both SLN and NLC are characterized through SEM, TEM, DLS, NMR, and AFM.

Lipid drug conjugates or LDC are created with a specific end goal to extend appropriateness of lipid-based transporters to lipophobic tranquilize atoms (Irby et al. 2017). It is the best alternate of hydrophilic drug conjugated SLN-based drug delivery with 33% drug loading capacity with regard to the lipid matrix used in nanocarrier formation (Wissing et al. 2004). Stability and targeted delivery of lipid based drug carriers are further functionalized and decorated with PEG, polyethylene oxide, polyoxamer, and poloxamine to increase the longevity of drug conjugate in a biological system (Dolatabadi and Omidi 2016).

Numbers of study have been conducted on lipid-based nanocarriers and their application in drugs and nucleotides targeted delivery, specifically dermal and oral delivery, due to their high biocompatibility and less toxicity at a very minimal amount. Katare and colleagues have synthesized non-steroidal anti-inflammatory drug diflunisal (DIF) conjugated SLN nanocarriers and studied therapeutic response in mice air pouch model, ear edema and rat paw edema model of rheumatoid arthritis (Kaur et al. 2016). Similarly, COX-2 inhibiting drug, celecoxib (CXB), associated SLN nanocarriers demonstrated a reduction in adverse systemic complications of only CXB use along with high drug entrapment capacity in a rat model of RA (Nirbhavane et al. 2018).

In direction of polymeric SLN-based delivery, resveratrol-loaded lipid carrier decorated with *N*-trimethyl chitosan graft palmitic acid (TMC-g-PA) was reported in sustained release in the gastrointestinal environment along with lesser toxicity which can be applied in gastric diseases (Ramalingam and Ko 2016). In another study, olmesartan medoxomil (OLM), an antihypertensive drug, conjugated SLN have reported enhanced bioavailability and drug release in male Sprague Dawley rats (Nooli et al. 2017). Similarly, Hasnain et al. have also developed OLM associated NLC and assessed their improved release kinetics as well as oral bioavailability in mice model (Hasnain et al. 2018).

Another study focused on tobramycin-loaded SLN (Tobra-SLN) nanoparticles and studied pharmacokinetics after topical and intravenous administration to the ocular region of rabbits (Chetoni et al. 2016). They also studied the improved antibacterial activity of Tobra-SLN along with their retinal and phagocytic cell penetration capacity. Similarly, propranolol hydrochloride-loaded NLC also exhibited improved permeation and prolonged contact time in rabbit ocular system (Sharif Makhmal Zadeh et al. 2018).

Further improvement of SLN-based delivery system, researchers biofunctionalized the SLN nanocarriers to achieve significantly improve drug payload and reduced toxicity. Sangamwar and colleagues have designed tamoxifen (TMX)-loaded α-lipoic acid-stearylamine (ALA-SA) conjugated SLN and observed enhanced bioavailability in anticancer treatment with minimum adverse reactions (Dhaundiyal et al. 2016). In another study lidocaine-loaded tocopheryl polyethylene glycol 1000 succinate (TPGS) conjugated lipid nanocarrier demonstrated prominent permeation efficiency and anesthetic effect for future perspective of topical local anesthetic therapy (Zhao et al. 2016).

After the advancement in almost every field of medical science, lipid-based nanocarriers have reported their importance in neural disorders. Recent study on nicotinamide-loaded phosphatidylserine (PS) functionalized SLN was reported to reduce tau hyperphosphorylation along with low cytotoxicity and improved biodistribution to brain cells of rat model of AD (Vakilinezhad et al. 2018). Similarly, chitosan hydrogel-based temozolomide-loaded SLN (TMZNLCHG) reported targeted controlled delivery to brain along with improved BBB transport (Khan et al. 2018). Ana et al. also used carbamazepine (CBZ)-loaded chitosan functionalized SLN nanocarriers which displayed excellent intestinal permeability and biodistribution for preclinical treatment of epilepsy (Ana et al. 2019). In another recent study, stearic acid-based SLN nanocarrier encapsulated methylthioadenosine (MTA) was used in treatment of cuprizone-induced demyelination model of mice that mimic the multiple sclerosis and histopathological evidences supported neural remyelination and kinetic study proved improved bioavailability (Kumar et al. 2019).

Due to their biocompatibility and low toxicity, lipid based nanocarriers are all over the healthcare market. Cyclosporin A and difluprednate loaded lipid emulsion marketed with name of Restasis® (Allergen Healthcare, USA) and Durezol™ (Alcon, Fort Worth, Texas, USA) for dry eye syndrome and ocular inflammation treatment, respectively, though Cyclosporin A loaded Cyclokat® (Novagali Pharma S.A) and latanoprost loaded Catioprost® (Glaucoma, USA) are in clinical trial phase III (Gan et al. 2013). Similarly, immunosuppressant sirolimus (Rapamune®, Wyeth Pharmaceuticals Elan Drug Delivery), megestrol acetate (Megace ES®, Par Pharmaceuticals Elan Drug Delivery), aprepitant (Emend®, Merck-Elan Drug Delivery), fenofibrate (Tricor® and Triglide® by Abbott Laboratories and SkyePharma-First Horizon respectively) and 2-methoxy estradiol, an estrogen metabolite (Panzem NCD, EntreMed Inc.) based nanosuspensions, were marketed in healthcare (Desai et al. 2012). Nanobio Corporation also has nanoemulsions based NB-001 and NB-002 compounds in clinical trial I/II for treatment of herpes labialis and onychomycosis (Zhang et al. 2008).

18.6.6 Liposomes

Liposomes are spherical vesicle having at least one lipid bilayer and can be produced by disruption of biological membranes (by sonication) (Pattni et al. 2015; Zylberberg and Matosevic 2016). These are nano/miniaturized scale specific or colloidal carrier, typically with 80–300 nm, size (Soni et al. 2016). One of the recognizing highlights of liposomes is its lipid bilayer structure, which mocks plasma membranes and can promptly combine with irresistible pathogenic organisms. By combining with bacterial films, the medication payloads of liposomes can be discharged to the plasma membrane or the inside of the microbes (Sercombe et al. 2015) Basically, liposomes are the concentric lipid bilayers, made up of phospholipid vesicles that enclose discrete aqueous space which may contain the transporting drug or compound. The most common phospholipids used in liposomes development are phosphatidyl choline (Lecithin)-PC, phosphatidyl ethanolamine (cephalin)-PE, phosphatidyl serine (PS), phosphatidyl inositol (PI) and phosphatidyl glycerol (PG) (Chang and Yeh 2012) (Daraee et al. 2016). These phospholipids should have gel state [human body temperature (T) < phase transition temperature (T_M)] to avoid drug or compound leakage in body and improve liposomal stability (Pattni et al. 2015). The flip-flop nature of phospholipids can also be stabilized through incorporating cholesterol at different concentration during drug loaded liposomal synthesis for sustainable drug release (Pattni et al. 2015). Their selective permeability, biodegradability, and osmotic sensitivity make them valuable in targeted nucleotide and drug delivery (Daraee et al. 2016). Other than conventional liposome preparation methods, like thin lipid film hydration method and reverse-phase evaporation technique, several other novel method like micro-hydrodynamic focusing (MHF), supercritical reverse-phase evaporation (SRPE) method, supercritical antisolvent (SAS) method and spray drying techniques are also in use (Pattni et al. 2015). These unique liposomes can be characterized through dynamic light scattering (DLS), size exclusion chromatography (SEC), nuclear magnetic resonance (NMR), transmission electron microscopy (TEM), cryogenic-TEM (Cryo-TEM), and atomic force microscopy (AFM) (Pattni et al. 2015).

Due to effective biocompatibility and less toxicity, liposomes and lipid-based nanocarriers abundantly used as nanocarriers in therapeutics and well as real-time imaging in rodents model. In recent years, their gradual increased use has also reported among researchers worldwide. Xin et al. showed improved cellular uptake and antitumor activity of DOX-loaded chitooligosaccharides (COS) modified liposomes in osteosarcomas MG63 cell-bearing nude mice model (Qi et al. 2016). Similarly, DOX-loaded PEGylated hyaluronic acid (HA) functionalized liposomes were also reported to improve osteosarcoma chemotherapy treatment. This study demonstrated HA-controlled redox reaction in improved cytoplasmic drug delivery along with low cytotoxicity and enhanced drug biodistribution at minimal drug-loaded nanocarriers administration (Chi et al. 2017). Similarly, hydrophilic moxifloxacin hydrochloride loaded hyaluronic-acid-modified liposomal hybrid nanoparticles (HA-LCS-NPs) were also reported to increased corneal permeability and ocular bioavailability in ocular delivery in rabbits (Liu et al. 2018). They also performed pharmacokinetic study of synthesized liposomal nanocarrier and prolonged precorneal retention along with excellent ocular tolerance was obtained.

Other than drugs or nucleotides transport, liposomes were efficiently proved themselves as excellent transport carriers. Rajadas and colleagues have demonstrated cardiac adipokine, [Pyr1]-apelin-13 polypeptide, transport through PEGylated liposomes which resulted into prolonged stability and effective working of adipokine in mouse model of pressure-induced heart failure (Serpooshan et al. 2015). In another study, luteolin loaded vitamin E d-α-tocopherol acid and PEG-1000 succinate (TPGS)-coated liposomes demonstrated improved cellular uptake along with increased Bax/Bcl-2 ratio-based increased apoptosis to inhibit tumor cell growth without altering morphological or physiological functions of nearby cells of lung cancer rodent model (Li et al. 2015). Similarly, Kaminskas and colleagues have used phosphatidylcholine and tristearin functionalized liposomes and SLN nanocarriers, respectively for transport in lungs (Li et al. 2015). They studied pulmonary pharmacokinetic behavior and lung clearance patterns of associated liposomes in upper respiratory tract of rodents. Venkatesh and his colleagues have also designed RGD polypeptide functionalized liposome-protamine-siRNA (LPR) based nanocarrier system to target P3F to reduce tumor cell growth in rabbit model of alveolar rhabdomyosarcoma (ARMS) (Li et al. 2015).

Several studies have been focused on use of biocompatible and further functionalized liposomes as a drug or si/mi-RNA carriers for treatment of CNS disorders. Montaner and colleagues reported simvastatin-loaded liposomes in treatment of transitory middle cerebral arterial occlusion (MCAOt)-based animal model of ischemic stroke (Campos-Martorell et al. 2016). They provided promising strategy for drug transportation through BBB without loss of path and targeted delivery in clinical samples. In another study to show dual mobility of liposomal nanocarrier, a study has demonstrated docetaxel (DTX) and quantum dots (QDs) loaded RGD conjugated TPGS liposomes in theranostic purpose in neural disorders (Singh et al. 2016). They reported ROS-induced sustained targeted drug release in brain without any adverse events.

In continuation of drug delivery, proteins and nucleotides were also reported in liposome-based targeted drug delivery to brain. One study of Chen et al. has reported tumor cell inhibition in animal model of glioma while treating with peptide-22 and cyclic RGD functionalized liposomes without any BBB restriction (Chen et al. 2017). They also demonstrated higher liposomal distribution onto tumor cells to give enhanced imaging resolution as well as improved drug delivery. In another study, researchers combinedly modified DOX-loaded liposomes with linked cyclic RGD (c(RGDyK)) and p-hydroxybenzoic acid (pHA) and used them in gliomablastoma cells (Belhadj et al. 2017). Their study proved efficiency of Y-shaped targeting liposomal nanocarriers with low cytotoxicity in in vivo and in vitro glioma cells. Recently, Singh and his colleagues have demonstrated importance of GEF-encoded pDNA-loaded transferrin (Tf) and penetratin (Pen) dual-functionalized liposome in treatment of neural cells in neurodegenerative diseases (dos Santos et al. 2018). They studied immunofluorescence measurements of transfected mice and reported no neural damage in mice brain which could have used in clinical subjects with any hurdle.

Several researches have been conducted and many more patents have been granted to liposomes based drug delivery system in human. For the first time, FDA has approved HSPC (hydrogenated soy phosphatidylcholine): Cholesterol: PEG 2000-DSPE (distearoyl-sn-glycero-phosphoethanolamine) coated doxorubicin (Doxil®) by Sequus Pharmaceuticals, USA, in 1995 for treatment of ovarian, breast cancer and Kaposi's sarcoma (Bulbake et al. 2017; Chang and Yeh 2012). In continuation of this, NeXstar Pharmaceuticals, USA, and Elan Pharmaceuticals have developed doxorubicin loaded DSPC (distearoylphosphatidylcholine)-cholesterol (DaunoXome®) and EPC (egg phosphatidylcholine): cholesterol (Myocet®) for AIDS-related Kaposi's sarcoma and metastatic breast cancer, respectively (Bulbake et al. 2017; Chang and Yeh 2012). In continuation of cancer therapy, amphotericin B conjugated DMPC (dimyristoyl phosphatidylcholine): DMPG (dimyristoylphosphatidylglycerol) (Abelcet®), HSPC:DSPG (distearoylphosphatidylglycerol): Cholesterol:Amphotericin B (Ambisome®) and Cholesteryl sulfate:Amphotericin B (Amphotec®) were developed by Sigma-Tau Pharmaceuticals, USA; Astellas Pharma, USA, and Ben Venue Laboratories Inc., Bedford, OH, USA, respectively, in late years of decade 1990 for treatment of fungal infection (Bulbake et al. 2017). Similarly, Takeda Pharmaceutical Limited and Talon Therapeutics, Inc., USA, have marketed mifamurtide-loaded DOPS (dioleoylphosphatidylcholine): POPC (palmitoyloleoylphosphatidylcholine) based Mepact® and vincristine loaded SM (sphingomyelin)cholesterol Marqibo® in non-metastatic osteosarcoma and Acute lymphoblastic leukemia therapy (Bulbake et al. 2017). In continuation of cancer therapy, DSPC (distearoylphosphatidylcholine):MPEG (methoxy polyethylene glycol)-2000:DSPE (distearoyl-sn-glycero-phosphoethanolamine) coated irinotecan (IRI) (Onivyde™) was developed by Merrimack Pharmaceuticals Inc. in fluorouracil and leucovorin-based combination therapy in metastatic adenocarcinoma of the pancreas (Bulbake et al. 2017). After the successful commercialization of liposomal based drug therapy, Novartis, AG, Switzerland has developed Verteporphin:DMPC and egg phosphatidyl glycerol (EPG) coated verteporphin drug conjugate for photodynamic therapy in choroidal neovascularisation and marketed the product as Visudyne®, which decreased moderate and severe vision loss in patients (Bulbake et al. 2017; Chang and Yeh 2012). Pacira Pharmaceuticals, Inc., Parsippany, NJ, USA, and SkyPharma Inc. have also developed morphine sulfate and bupivacaine-loaded liposomes for pain management on the name of DepoDur™ and Exparel® (Bulbake et al. 2017; Chang and Yeh 2012). In the treatment of viral infection, Epaxal® and Inflexal® V came into the market and patented by Crucell Berna Biotech, Switzerland. These liposomal vaccination technology were designed by 75:25 molar ratio of DOPC (dioleoylphosphatidylcholine):DOPE (dioleoly-sn-glycero-phophoethanolamine) in treatment of Hepatitis A and influenza with improved efficacy, tolerability, and immunogenicity over other conventional vaccination (Bulbake et al. 2017; Chang and Yeh 2012). After successful commercialization of liposomal-based drug therapy, researchers have pushed themselves for more safe and effective drug development, and therefore, several liposomal-based drugs are in clinical trials. For example, LEM-ETU (mitoxantrone) in cancers, liposomal Grb-2 [antisense oligodeoxynucleotide growth factor receptor-bound protein 2 (Grb-2)] in hematologic malignancies, INX-0125 (vinorelbine tartrate), INX-0076 (topotecan) and SGT-53 (p53) in solid-state tumor, Alocrest (vinorelbine) in breast and lung cancer; these are compounds are in clinical trial phase I (Bulbake et al. 2017; Chang and Yeh 2012). Similarly, aroplatin, SPI-077, OSI-211, S-CKD602, endotag-I and atragen are in phase II of a clinical trial lead by top pharmaceutical industry like Agenus Inc., Alza Corporation, NeoPharm Labs Ltd., Medigene and Aronex Pharmaceuticals for various types of cancer (Bulbake et al. 2017; Chang and Yeh 2012). After the successfully completion of phase I and II, tecemotide-loaded stimuvax, Prostaglandin E-1 (PGE-1)-loaded liprostin and cisplatin-loaded lipoplatin liposome-based drug therapy are in clinical trial phase III for treatment of lung cancer, restenosis after angioplasty and non-small cell lung cancer (Bulbake et al. 2017; Chang and Yeh 2012).

18.7 Regulation of Nanomedicine in India

Advancement in nanotechnology based drug delivery not only painted bright colors in research as well as common therapeutic use, but it also increase the concern about toxic material used in nanotechnology and biological system safety. According to Allied Market Research, the current status of global nanomedicine market is 111,912 million dollars in which India acquired third position followed by China and USA with compound annual growth rate (CAGR) of 13.4% between years 2016–2023 (The Nano Approach of Medicines; February 08, 2018; Opinion By Manbeena Chawla; https://www.biospectrumasia.com/opinion/29/10291/the-nano-approach-of-medicines.html). After FDA and European Medicines Agency (EMA) approval of Doxil®, Myocet® and Mepact® type pharmaceuticals in healthcares, India understood the importance of nanomedicine in field of medicine as well as economical growth. Currently, only 16 nanoformulated drugs are in Indian market for treatment various diseases and their management.

The first step for nanomaterial use in R&D and their management based regulation was taken through National Nanotechnology Initiative (NNI) by USA in 2001, which not only focuses on nanosciences for national economical growth, it also target their use for common public in healthcare. In Indian scenario, Planning Commission of Government of India supported several nanotechnology based R&D program for 9th five-year plan (1998–2002). Later the Department of Science & Technology (DST) launched “Programme on Nanomaterials: Science and Devices” in 2000 to support nanomaterial-based research (Sundararajan and Rao 2012). In continuation of these events, DST announced nanotechnology focused research through implementing National Nanoscience and Nanotechnology Initiative (NSTI) in October 2001. It also set up an expert group on “Nanomaterials: Science and Devices” in 2001–2002, which supported nanopharmaceutical-based basic and applied research. But the most important program of nanotechnology-based research was initiated by DST in year 2007 as “Mission on Nano Science and Technology (Nano Mission)” under the regulation of Nano Mission Council (NMC) along with technical help of Nano Science Advisory Group (NSAG) and the Nano Applications and Technology Advisory Group (NATAG). After implementing all these programs, Indian government announced few modification in laws regarding human and environmental safety, and some of them are

1. Drugs and Cosmetics Act, 1940, National Pharmacovigilance Protocol, Medical Devices, Regulation Bill, and Insecticides Act, 1968, for production and marketing of nanotechnology-based materials and drugs.
2. Factories Act, 1948 and OHS under other legislation for Occupational Health and Safety.
3. Pollution control laws, Environment Protection Act, and Public Liability Insurance Act for Environmental Risk Management.
4. Factories Act, Hazardous Material (Management, Handling and Transboundary Movement) Rules 2007, BioMedical Waste (Management and Handling) Rules 1998, Municipal Solid Wastes Rules 2000 for waste disposal.

Even after all these laws, only precautionary measurements are taken by research laboratories. Therefore, Nano Mission established golden standard for nanotechnology-based research which comes under National Regulatory Framework Road-Map for Nanotechnology (NRFR-Nanotech) (PIB 2014). After arguments have been debated, Indian government finally launched ethical guidelines on "Guidelines and Best Practices for Safe Handling of Nanomaterials in Research Laboratories and Industries" in year 2016 (http://nanomission.gov.in/What_new/Draft_Guidelines_and_Best_Practices.pdf). Every nanoscientists need to follow these guidelines; and industry based nanotechnology research will not get commercialization approval if guidelines and good laboratory practice (GLP) is not followed. This guidelines not only concerned for nanomedicine manufacturing process, it also focused on preclinical, clinical, and post-marketing studies along with quality and regulatory guidelines to be followed.

18.8 Conclusion

Nanotechnology has just transformed treatment at numerous levels and is profoundly changing the treatment design. Nanotechnology has potential to create novel materials and devices equipped with vast range of applications that have a remarkable effect on particular perceiving of the pathogens, directed drug transport, and conquering demerits of the regular therapies. Some nanotechnology based plans have just been propelled in the market and many are experiencing research and clinical trials. The harmful impacts of conventional therapies can extraordinarily be eliminated by these novel dynamic or passive directing of drug transport, which can considerably build the survival rate.

We have filtered last 10-year research conducted (Source: Pubmed; search terms "*drug delivery*" and "*liposome/dendrimers/CNT/liposome/lipid.*" Date of search: January 2019) on liposome, dendrimers, CNT, and polymer-based nanocarriers (Fig. 18.1), which concludes maximum research on liposomal based drug delivery in preclinical and clinical study. Though, fewer patents were granted for liposomal-based nanocarriers compared to carbon nanotube drug delivery system (Fig. 18.2). The patents were filtered to identify the total patents granted in year 2009–2019 (Source: Google patents. search terms "*patents* and "*liposome/dendrimers/CNT/liposome/lipid based drug delivery.*" Filtered from 2009–2019 and only "*granted patents.*" Date of search: January 2019). This demonstrated highest patents on CNT based drug nanocarrier followed by liposomes and polymeric nanoparticles. Even after all these data, toxicity and less biocompatibility of CNT enhanced use of liposomal-based drug delivery system in clinical trials and successful commercialization of the nanomedicine.

Even after advancement in nanoformulated drug delivery based research, several crucial steps need to be taken care of before the drug comes into market or clinical use. These steps involve understanding of compositions to be used to prepare nanocarriers, their pharmacokinetic properties, and laws and ethical guidelines

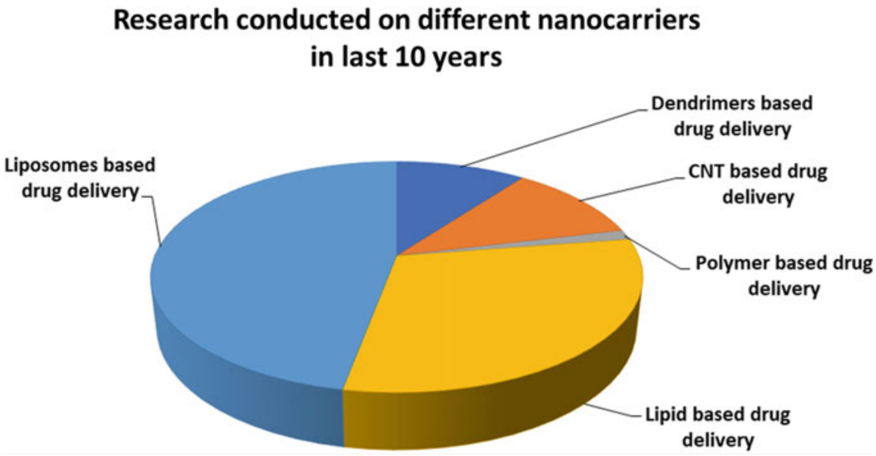

Fig. 18.1 Research conducted on different nanocarriers in last 10 years. *Source* Pubmed; search terms "*drug delivery*" and "*liposome/dendrimers/CNT/liposome/lipid.*" Date of search: January 2019)

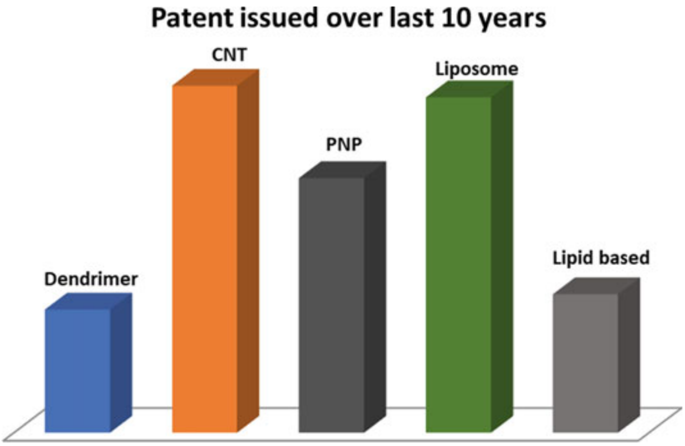

Fig. 18.2 Patents issued for different nanocarriers in last 10 years (2009–2019). *Source* Google patents. Search terms "*patents*" and "*liposome/dendrimers/CNT/liposome/lipid based drug delivery.*" Filtered from 2009 to 2019 and only "*granted patents.*" Date of search: January 2019

along with approval process from regulatory authorities. Therefore, every new research should carry out above steps for efficient and successful marketing of nanoformulated drug. Not restricted to this, the toxicity of nanomedicine can be reduced by use of the personalized therapy for specific patient group according to their genetic and disease profile. The size and morphological properties of nanomedicines along with its physiochemical nature can also be changed according to severity of disease and to achieve optimum benefits. However, there are several other issues still need to be addressed, such as understanding of pathophysiology of diseases, nanocarrier and drug conjugation study, their manufacturing, commercialization, and regulatory hurdles along with lower the complexity of nanomedicines for their translation in clinics.

18.9 Future Prospects

Nanotechnology has started to change the scale and techniques for various imaging, medication delivery and diagnostics. The NIH emphasizes 'Nanomedicine Initiatives' for nanoscale advances, which will start yielding more health advantages in next 10 years. This incorporates the advancement of nanoscale laboratory based symptomatic and medication revelation stage gadgets, for example, nanoscale cantilevers for microchip gadgets and nanopore sequencing. The National Cancer Institute has also projects with the objective of creating nanometer scale multifunctional substances which can analyze, convey remedial operators, and screen malignancy treatment advances. Nanotechnology also incorporates plans and designing of focused applications of specialists which enhances the growth of cells and thereby visualizing nanodevices equipped for various disease cells that make up a tumor inside a person. Besides, in order to evaluate the full in vivo capability of nanotechnology in focused imaging and medication, nanocarriers need to get more advanced through both physicochemical and physiological procedures. The framework of complex connections characteristics is sorted out by incorporating nano-vehicles which exhibit solidness to the microenvironment. For instance, changes in mitochondrial film potential (MMP) in Jurkat T cells after treatment with poly(ethylenimine), PEI. This treatment leads to the loss of MMP is an early occasion of apoptosis. Apoptosis was additionally affirmed by cytochrome c discharge from mitochondria and caspase 3 initiation. Implications of nanocarriers provides an excellent tool for extracellular and intracellular medication discharge rates in various pathologies, association with natural milieu e.g. opsonization. The implications of nanocarriers have significant advancements in anatomical, physiological, immunological or biochemical functions effecting infection states (e.g., tissue specific receptor articulation and escape courses from the vasculature). Characteristically, focusing on nanomaterial-based techniques may fluctuate in connection to the area of the illness because toxic quality issues of nanomaterials are of specific concern however are frequently overlooked. The organic nanobio materials are being viewed as generally more secure options. Because of their organic inception these materials can bio actively interacts with the cell parts and more valuable as quality conveyance. The utilization of lipidic and polymeric Nano biomaterials for formulation of quality-based medication particles are advancing. Therefore, it is crucial to evaluate research being carried out to address these issues if effective proficient utilization of these advancements will be accomplished. Lastly, the fate of nanomedicine will rely mainly on reasonable implications of nanotechnology materials and devices based incorporating organic procedures instead of constraining applications for a few materials.

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Chapter 19
Nanoparticles for Detection, Imaging, and Diagnostic Applications in Animals

Priya Mishra, Tanya Munjal and Sonu Gandhi

Abstract The conventional therapies and modalities have paved the way for the progress and advancement of comparatively finer technologies in the field of theranostics. The advents of nanotechnology have presented a much better alternative as they provide novel diagnostic and therapeutic approaches. This chapter describes the types of nanosystems available for detection, imaging, and treatment. Surface functionalization of nanomaterials makes them very flexible to use in biomedical applications and also enhances their target specificity, besides reducing the cytotoxicity which justifies their use for imaging and detection application in conventional techniques such as magnetic resonance imaging. The specificity of nanoparticles, alongside facilitating the imaging modalities, also helps in targeted treatment such as hyperthermia-based therapy. The introduction of different types of biosensor has made it easier to detect the disease at early stage and thus provide the patient an appropriate treatment timely. Therefore, this chapter puts forth the nanoparticle-based applications in detection, imaging, and diagnostics in animals.

Keywords Diagnostic · Therapeutic · Disease markers · Biomedical imaging · Nanobiosensor · Animals

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19.1 Introduction

Nanoparticles gain influence on the diagnosis, remediation, and avoidance of disease so as to trigger early-stage detection, besides being a pinpoint and reliable therapy due to their applications in diagnosis and therapy, molecular imaging, bio-detection of molecular disease markers, implant technology, tissue engineering and radionuclide delivery (Alharbi and Al-Sheikh 2014). Nanoparticles have shown tremendous potential for detecting various biomarkers when labeled with viruses fragment, distinct proteins, antibodies (Gandhi et al. 2008), and variant disease indicator (Alharbi and Al-Sheikh 2014). Due to unique size-dependent properties, nanomaterials are structurally and functionally prevalent in inorganic, organic, and biological fields and established themselves as superior and indispensable material (Alharbi and Al-Sheikh 2014). In order to treat the central nervous system (CNS) diseases, nanomaterials have improved the efficiency of drug delivery via micro-molecules across the blood–brain barrier (Krishnan and George 2014). The fact, that nanoparticles can accommodate, due to large surface area, a huge number and a wide range of functional groups that can be linked with multiple diagnostic and therapeutic agents, creates the opportunity to design nanoparticles with diverse functionalities which are used for multimodality imaging as well as for integrated imaging and therapy (Nie et al. 2007). The enhanced permeability and retention (EPR) effect makes the nanoparticles a viable aspirant to accumulate at the disease site (Chapman et al. 2013) which makes them an ideal candidate to be used as contrast agents in imaging modalities like the magnetic resonance imaging (MRI) technique (Kawadkar et al. 2011). This chapter aims at discussing types of nanoparticles, surface functionalization, and its prospects and relevance in imaging, diagnostics, and detection in animals.

19.2 Nanoparticles Categorization and Properties

Nanoparticles can be best understood as miniaturized particles in the nanoscale range with favorable physical, electronic, and optical properties. Various methods are available to compose nanoparticles and different types of nanoparticles are shown diagrammatically in Fig. 19.1. Based on the methodology used, nanoparticles, nanoshells, nanospheres as well as nanocapsules can be obtained (Pal et al. 2011). The fluorescence provided by the nanoparticles for imaging applications makes them highly advantageous (Sharma et al. 2010).

19.2.1 Quantum Dots (QDs)

QDs are miniaturized semiconductor nanocrystals with diameter ranging from 2 to 10 nm in diameter and consist of elements from groups II to VI or III to V and are

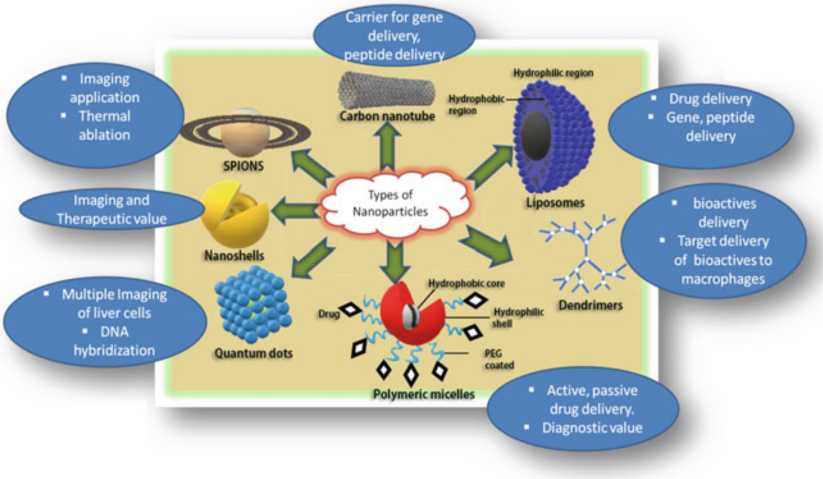

Fig. 19.1 Types of nanoparticles and its various applications. Based on physical and chemical characteristics, the nanoparticles can be categorized into carbon nanotube (CNT), liposomes, dendrimers, polymeric micelles, quantum dots (QDs), nanoshells, and superparamagnetic iron oxide nanoparticles (SPIONs) with application as carrier in gene delivery, drug delivery, imaging, and diagnosis, etc.

advantageous over traditional organic fluorescent dyes. Besides, they put forth a range of worthwhile attributes for spectroscopy, few of which includes long lifetime, elevated fluorescence intensity and good resistance to photobleaching (Fang et al. 2012).

Due to their peculiar nature corresponding to electronic and optical characteristics, quantum dots (QDs) are a subject under study for being a novel probe for biomedical imaging both in vitro and in vivo (Fang et al. 2012). The conjugation of nanoparticles with various biomolecules and peptides enhances their performance (Gandhi et al. 2016). For targeting molecules with high specificity and sensitivity, QD-based probes can be utilized in conjugation with bimolecular agents such as antibodies (Abs), peptides, or other small molecules (Fang et al. 2012). The tempo-spatial association among several biomarkers is revealed by QD-based multiplexed molecular imaging (Fang et al. 2012). QDs work on the principle of quantum confinement which says that when an object is confined to a small space then it can only occupy certain discrete energy levels. Several studies dealing with cancer imaging in mouse models have been conducted on QDs. QD-prostate-specific membrane antigen (PSMA) was used for whole animal cancer imaging and their study revealed the potential of QDs for prostate cancer diagnosis and real-time monitoring as QDs were very efficiently and uniformly distributed in prostate tumor (Fang et al. 2012). They used the near-infrared (NIR) QD-peptide conjugate to target glioblastoma and showed long duration of signals along with high signal to background ratio. Arginine-glycine-aspartic acid peptide-conjugated QDs to target integrin αvβ3 in a murine xenograft model. QDs facilitate easy integration of therapeutic components, targeting ligands, and multimodality imaging labels into single entity due to size plus the structural similarities between imaging and therapeutic nanoparticles (Fang et al. 2012). The utility of quantum dots in animal studies was also demonstrated by Liu et al. (2013) when their team performed the experimental study to determine the toxicity of silicon quantum dots in mice and monkeys. The test results were very encouraging as neither species showed any signs of toxicity even at high dose of 200 mg/Kg and there was no change recorded in the blood chemistry which strengthened the fact that quantum dots are revolutionary in the field of drug delivery and neuroimaging because they do eliminate the risk of neurotoxicity.

Size-dependent discrete energy levels are also exhibited by semiconductor QDs, besides justifying their ability in biomedical fields due to their optical properties (Malik et al. 2013). The aforesaid energy gap shows an inverse relation with the size of nanocrystal, thus producing a size-dependent rainbow of colors (Malik et al. 2013). QDs emerge as an extremely suited option for the synchronous examination of multiple events and molecules because light wavelengths from ultraviolet (UV) to infrared (IR) region can be attained with compositional and dimensional variations (Malik et al. 2013).

In the present biological world, QDs emerge as an alternative fluorescent probe because the application of traditional fluorophores, e.g., organic dyes and fluorescent proteins is limited. This is due to their narrow absorption range, broad emission spectra, and short fluorescent lifetimes, whereas QDs exhibit broad absorption and narrow emission spectra and show low susceptibility to photobleaching than organic dye molecules for the reasons of their inorganic composition (Malik et al. 2013).

19.2.2 Super Paramagnetic Iron Oxide Nanoparticles (SPIONs)

Magnetic nature of Fe_2O_3 particles has been a great asset for imaging modalities (Tomitaka et al. 2015). The superparamagnetic iron core possessed by superparamagnetic iron oxide nanoparticles (SPIONs) makes them useful as contrast agents for magnetic resonance imaging or MRI and also utilized for targeted delivery (Thomas et al. 2013). Parameters like shape, composition, and surface coating are chief factors in determining the magnetic and biological behaviors of SPIONs (Revia and Zhang 2016). The dimension of iron oxide nanoparticles (IONPs) in nanoscale provides a high surface area-to-volume ratio, consequently resulting in large surface energies (Revia and Zhang 2016). In MRI, a large external magnetic field is applied to the test sample which leads to alignment of magnetic moments of protons within the sample and magnetic moments of the SPIONs couple with the magnetic moments of adjoining protons causing spin dephasing and reduced relaxation times of protons in the vicinity (Revia and Zhang 2016). Detection of SPIONs can be done with high sensitivity, and both the iron and polymer components of SPIONs are biocompatible and degradable which adds up to their advantage (Thomas et al. 2013). The dimension corresponding to iron oxide nanoparticles holds a crucial role in target cell uptake and elimination from the body. To accommodate targeting, the surface properties of these nanoparticles can be modified (Thomas et al. 2013). SPIONs are employed as an MRI contrast agent because the T2 relaxivity of SPION-based agent is far more than that of gadolinium agents and the physiochemical properties of SPIONs, such as size, charge and surface chemistry, affect the stability, biodistribution, and metabolism (Thomas et al. 2013).

Thomas et al. (2013) fabricated MRI/optical dual-contrast agents for in vivo cancer imaging by thermally cross-linking SPION with the help of Si-OH containing copolymer. Cy5.5 dye was conjugated to SPION after amine alteration for imparting optical imaging properties. The Cy5.5-labeled SPION was tested in Lewis lung carcinoma-bearing mice and resulted in a tumor-specific T2 signal drop of 68% in MRI, with fluorescence lasting up to 4 h in optical imaging. The results showed the specific accumulation of Cy5.5-SPION in the tumor. A water-soluble, SPION-based nanocarrier was developed to target a tumor with integrin αvβ3 expression. SPIONs were PEGylated by cyclic Arg-Gly-Asp-D-Phe-Cys (cRGD) peptides. The MRI relaxivity for cRGD-conjugated SPION was found to be lower than that for clinically existing IONPs. Andreas et al. (2012) showed the applicability of SPIONs in highly sophisticated imaging application like the MRI with high efficiency. The team used citrate-coated SPIONs and employed the same for magnetic stem cell labeling which could have never been possible without the definite specificity and selectivity of the SPIONs. The other encouraging finding was that no significant cytotoxicity was observed which open up another advantageous realm of the SPIONs. The team stamped the applicability of the SPIONs in imaging and labeling applications successfully. Ali et al. (2017) also demonstrated in their study that the SPIONs are highly efficient contrast and imaging agents. The experimental demonstrations were performed on the BALB/c mice models using polymer-based SPIONs that were employed as T_2 magnetic resonance contrast agents and their toxicity was also studied. The polymer-coated SPIONs yielded a better contrast result as compared to Endorem. However, both Endorem- and polymer-coated SPIONs showed no toxicity up to at least 60 days upon injection and did not produce any significant lesions. The conclusion of the experimental analysis puts forward the SPIONs as a powerful diagnostic tool having non-significant cytotoxicity.

SPIONs provide real-time treatment monitoring of therapeutic drug delivery as well as tissue response and thereby improves a patient's quality of life (Revia and Zhang 2016). SPIONs were used to label murine dendritic cells in order to track their migration in vivo with non-invasive MRI. Dendritic cells induce enhanced anti-tumor immune responses by stimulating effector T cells (Revia and Zhang 2016). The study showed that the SPION-labeled dendritic cells provided a visualization of the drug localization, thereby informing about the relative effective dosage that was received and that the appropriate delivery site was accessed.

19.2.3 Carbon Nanotubes (CNTs)

Carbon nanotubes are greatly useful in applications of disease detection and monitoring (Tey et al. 2010). These unique nanoparticles have gained great attention and interest during past years due to their unique mechanical properties along with highly desirable electrical and thermal properties besides providing for the possibility of getting their surface functionalized with a wide group of bio-conjugates that paves the path for their numerous therapeutic and drug delivery applications (Sanginario et al. 2017). CNTs are an allotropic form of carbon and their structure consist of a single rolled-up graphene sheet whose diameter ranges from few nanometers to hundreds of nanometers. CNTs are divided into two main groups: single-walled carbon nanotubes (SWCNTs), which consist of only one wrapped up graphene sheet and multi-walled carbon nanotubes (MWCNTs), in which more than one sheet is wrapped in a concentric fashion (Sanginario et al. 2017).

CNTs are poorly soluble and have the tendency to form aggregates, due to hydrophobic nature, in aqueous medium due to which their application gets limited in almost all biological medium (Sanginario et al. 2017), however, this limitation can be overcome through appropriate surface functionalization that has attracted widespread interest in last few years as it augments the application domain of the CNTs (Sanginario et al. 2017).

CNTs have the potential to be more than just a drug carrier as they can be engineered as excellent adjuvant contrast agents (CA) that can be used for many different imaging techniques (Sanginario et al. 2017) like ultrasonography, one of the most popular imaging techniques, that is associated with low price per examination and intrinsic safety (Sanginario et al. 2017). Photoacoustic (PA) imaging is another powerful imaging technique, like ultrasonography, in which the imaging signal output, in the form of acoustic waves, are generated with the source light inducing regions of tissue to become an active acoustic source (Sanginario et al. 2017). Pristine CNTs have been found to possess adequate PA properties and hence can be easily functionalized for activity enhancement. However, it is a challenge to target CNTs at the diseased site for imaging purpose (Sanginario et al. 2017), but, since they possess the properties of intrinsic fluorescence along with strong optical absorption in near-infrared (NIR) (700–700 nm) region, hence, they have the potential to be used and employed as non-photobleaching fluorophores that have high-resolution in in vivo imaging (Sanginario et al. 2017).

Besides unique physical properties, both MWCNTs and SWCNTs have the capability to show strong optical absorption in near-infrared (NIR) region that can be used for thermal destruction of the diseased cells (Liu et al. 2011). Upon irradiation by NIR light (700–1000 nm), which is a tissue transparency window ideal for optical imaging and phototherapies, CNTs generate heat by light absorption upon being irradiated by NIR light and thus induce and trigger thermal destruction of diseased cells that contain significant concentrations of CNTs which accumulate at the site due to high selectivity (Liu et al. 2011). Functionalized CNTs, upon intravenous injection into the animals (e.g., mice, rats), accumulate in the reticuloendothelial system, which includes the liver and spleen, and thus gradually gets excreted that eventually halts the debate on the clearance mechanism of nanotubes (Liu et al. 2011). Unlike non-functionalized and raw CNTs, well-functionalized CNTs conjugated with biocompatible coatings (e.g., by PEGylation) have shown reduced in vivo toxicity after they are intravenously injected into animals. However, the mechanism through which they affect the fertility and induced immune responses after they are administered has only been partially studied and needs future attention (Liu et al. 2011). The CNTs have, however, been shown to be nontoxic in nature which is a big advantage while considering it as an option for drug delivery and diagnostic tool. Schipper et al. (2008) used a sample of mice to show that the CNTs have nontoxic effects. The mice were 8–12-week old which is the most prominent animal test sample considered for cancer research and analysis. The experimental data recorded over a span of 4 months showed no signs of cytotoxicity in the clinical, laboratory, or the survival parameters of the sample. The mice sample had age-related changes only which were evident after killing. The single-walled CNTs were found to be persisting in liver and spleen without traces of toxic effects. The targeted drug delivery capability of the CNTs has also been proved by the researchers using animal models apt for the study. Bhirde et al. (2009) used mice model to demonstrate the killing of cancerous cells, in vitro and in vivo, by employing single-walled CNT system. The SWCNTs were functionalized with cisplatin and epidermal growth factor (EGF) to provide specificity against the squamous cancer cells. The SWCNT-EGF bioconjugate was found to be highly efficient in internalizing into the cancer cells and was shown to be better than bioconjugate without EGF. The experimental analysis revealed that the SWCNT-EGF bioconjugate was selectively taken up by the cancerous cells which led to highly targeted approach. The tumor regression was found to be significantly high in the case of SWCNT-cisplatin-EGF bioconjugate which establishes the fact that CNTs provide a highly targeted and dedicated platform for drug delivery. The capability of CNTs to facilitate for targeted delivery and high selectivity was also proved by Zerda et al. (2010) when his team established the utility of the CNTs in the field of photo caustic molecular imaging in live mice sample. Single-walled CNTs were used after being functionalized with indocyanine green dye. The enhanced contrast agent was further conjugated with cyclic Arg-Gly-Asp (RGD) peptides in order to target $\alpha_v\beta_3$ integrins that are linked with tumor angiogenesis. The performance of the tumor-targeted contrast agent was compared with that of the non-targeted contrast agent after the agents were intravenously injected into the test subjects. The targeted contrast agent was found to be highly efficient and gave around 300 times higher photo caustic contrast in the living cells of the test animal than the previously reported SWCNTs. The team also reported that the novel agent had the capability to detect nearly 20 times fewer cancer cells as compared to previously reported SWCNTs. These studies stamp the utility of the CNTs in the field of molecular imaging and diagnostics through targeted and selective approach.

19.2.4 Nanoshells

Metal nanoshells are novel spherical nanoparticles which have a dielectric core that is covered by thin metallic shell, typically of gold (Loo et al. 2004). Nanoshells have shown highly desirable optical and chemical properties that are needed for success in biomedical imaging and therapeutic applications (Loo et al. 2004). Methods like the use of radio-immuno conjugates have certain limitations such a slow tumor uptake, dose-limiting toxicity, and the inherent necessity to expose patients to potentially harmful ionizing radiations (Loo et al. 2005). While nanoshells provide an effective alternative way that enables dual imaging/therapy applications as they can be successfully engineered and modified in order to attain desirable scattering and absorption properties at particular frequencies (Loo et al. 2005). The selective accumulation of nanoshells at the diseased site is made possible and easy by the enhanced permeability and retention (EPR) of small particles (<400 nm) that are associated with the leaky vasculature of the diseased tissue (Loo et al. 2005). Enhanced targeting and effectiveness is achieved by using antibodies that facilitate targeting against the overexpressed cells that are present in the diseased surfaces (Loo et al. 2005). Besides being capable of highly targeted and specific drug delivery, nanoshells also have the desirable property by the virtue of which they provide molecule-specific image contrast and are capable of mediating treatment that is based on NIR thermal ablation therapy (Loo et al. 2005). Nanoshells have proved themselves to highly useful in the role of valuable contrast agents that are used for imaging modalities which are based on photonics such as reflectance confocal microscopy (RCM) and optical coherence tomography (OCT). Since these approaches offer high-resolution technology for the early detection facilitated by the high scattering optical cross-section, the nanoshells present themselves to be a suitable option for early disease detection tool. Loo et al. (2005) used nanoshells and targeted them against HER2 biomarker that is associated with SKBr3 breast cancer and thereby performed the combination therapy. The scatter-based optical contrast significantly increased when compared to control cell groups which was due to the nanoshells getting bound to the cells that were incubated with anti-HER2 nanoshells. Cell death caused by the photothermal therapy was observed in cells that were treated with NIR laser and that were exposed to anti-HER2 nanoshells, while it was no observed in the cells that were treated with only nanoshells conjugated to non-specific antibody or NIR light. The applicability and utility of the nanoshells as a powerful diagnostic tool was presented by Dickerson et al. (2008) when his team used mice model for performing the near-infrared plasmonic photothermal therapy (PPTT). The procedure was used against the squamous cell carcinoma in the test subjects. The nanoshells were functionalized with PEG and were administered directly and intravenously. The xenografts for the squamous cell carcinoma in test animals showed a drastic decrement in the size upon administration of the pegylated nanoshells (gold nanorods). The effects of both administration methods were studied for 13 days and dramatic inhibition in the tumor growth was observed. The surrounding tissues suffered minimal damage which speaks for the specificity of the nanoshells.

Metallic nanoshells provide a huge advantage of variable optical resonance that can be precisely varied over a broad spectrum which ranges from UV to mid-infrared, including, thereby, the NIR region where the transmissivity reaches its peak (Loo et al. 2004). Besides providing better spectral tenability, in comparison to conventional organic dyes, nanoshells also ensure decreased susceptibility to chemical and thermal denaturation (Loo et al. 2004).

After they accumulate at the diseased site, nanoshells mediate the treatment based on NIR thermal ablation therapy and provide a highly desirable molecule-specific image contrast that makes the task all the more easy (Loo et al. 2005). Nanoshells are important because they present an alternate method that would enable dual imaging/therapy applications as they have the capability to be engineered in a way to provide both scattering and absorption properties at particular frequencies (Loo et al. 2005).

19.2.5 Polymer Nanoconjugates

Polymeric nanoparticles consist of dissolved, entrapped, and encapsulated drug in a nanoparticle matrix which possess a range of diverse properties and release characteristics. Vesicular systems of nanoparticles represent a cavity surrounded by unique polymer membranes, whereas the nanocapsule or nanospheres contain drugs in a uniformly dispersed manner while the vesicular systems comprise of a cavity that is surrounded by unique polymeric membranes.

The targeting of most of the drugs in the body remains inefficient because they get distributed very fast and only a fraction reaches the desired site. This limitation can be overcome, and the bioavailability of the drugs can be augmented successfully by conjugating nanoshells with high molecular weight polymers that eventually slow down the renal elimination process, thereby increasing the circulation time and hence ensuring better response (Dragojevic et al. 2015). The disorganized vasculature and poor lymphatic drainage of the diseased site are utilized for producing EPR effect which in turn enhances the targeted drug delivery capacity of these water-soluble macromolecular drug carriers (Dragojevic et al. 2015). Since the polymer-bound drugs accumulate within the diseased site by the virtue of the EPR effect, therefore higher doses can be applied to improve therapeutic outcomes (Dragojevic et al. 2015).

Polymers must be well characterized and should be synthesized reproducibly in quantities and purity that is acceptable for clinical applications so as to optimize their potential as drug carriers (Dragojevic et al. 2015). It is of utmost importance that they contain appropriate functional groups that are needed for incorporation with specific drugs besides being composed of materials that are biocompatible, non-immunogenic, and biodegradable so that they remain stable in circulation and release their chemodrug cargo intracellularly while maintaining a low variability in the particle size distribution which is necessary to ensure homogeneity of the polymer–drug conjugates (Dragojevic et al. 2015). Since proteins have shown favorable interactions with respect to the applications in the biomedical field (Mahendra Wijaya et al. 2009), they have the required potential to meet all the requirements and thus synthetic, natural, and genetically engineered protein polymers can contribute massively to contemporary drug delivery technology (Dragojevic et al. 2015). Verma et al. (2012) evaluated the efficacy of the pectin–cisplatin polymeric nanoconjugate in B-16 mouse model. The results showed an enhanced blood circulating levels for cisplatin. The nanoconjugates exhibited an elevated plasma residence and enhanced half-life of cisplatin. The team reported that almost insignificant accumulation of cisplatin was seen in the kidneys that facilitates for decreased nephrotoxicity. The in vivo study was done through solid tumor models and the anti-tumor response ad efficacy was monitored and recorded by getting a measure of the tumor burden. The in vivo and in vitro studies carried out on the mouse model against the melanoma cells established high efficacy for the polymeric nanoconjugates.

19.2.6 Micelles

Micelles are colloidal particles ranging from 5 to 100 nm size and consisting of amphiphiles or surface-active agents (surfactants) that are comprised of two distinct regions: mostly hydrophilic head-group and a hydrophobic tail (Oerlemans et al. 2010). Although at low concentrations in aqueous solution, the amphiphiles exist as monomers but there is a concentration range in which the aggregation and self-assembly take place upon increasing the concentration and the particular value at which the micelles are formed is referred to as the critical micelle concentration (CMC) (Oerlemans et al. 2010). The dehydration of the hydrophobic tails leads to a favorable state of entropy which facilitates for the formation of micelles above their respective CMC (Oerlemans et al. 2010).

Polymeric micelles have several advantages over other counterparts, such as smaller size as compared to liposomes that help in the percutaneous lymphatic delivery and extravasation from blood vessels into the diseased tissue (Oerlemans et al. 2010). The polymers with hydrophilic and hydrophobic units that have the capability to self-assemble in an aqueous environment into sophisticated structures that are composed of hydrophobic core and stabilized by hydrophilic shell, form the basis for polymeric micelles. There are different possible ways to arrange these blocks: A-B type copolymers (diblock copolymer), A-B-A type copolymers (triblock copolymer), and grafted copolymers (Oerlemans et al. 2010).

Reduced absorption and intravenous administration are both challenging because the former leads to low bioavailability of drugs after oral administration while the latter requires a formulation consisting of organic solvents and classical surfactants (Oerlemans et al. 2010). Micelles have the potential to overcome these problems because solubilization of hydrophobic drugs in the core eases the task as these hydrophobic cores allow easy encapsulation of poorly soluble drugs by providing a natural carrier environment (Blanco et al. 2009).

In addition to passive targeting, micelles can be easily modified with ligands that facilitates for active targeting, that increases the selectivity of the NP system for the diseased cells, and enhances intracellular drug delivery besides simultaneously reducing systemic toxicity as compared to systemic chemotherapy (Oerlemans et al. 2010). Specific ligands, like monoclonal antibodies (mAbs) or their Fab fragments, oligosaccharides or peptides can be conjugated for achieving active targeting. The conjugated ligands allow the micelles to selectively bind to the receptors that are overexpressed on the diseased cells (Oerlemans et al. 2010).

Then, micelles get internalized by the endocytosis that in turn results in higher intracellular drug concentrations besides allowing the micelles to selectively bind to the respective antigens that are overexpressed on the diseased cells (Oerlemans et al. 2010). An actively targeted micelle-based drug delivery system was reported that consisted of Pluronic P85 along with murine polyclonal antibodies against α2-glycoprotein that were employed for the delivery of the neuroleptic agent haloperidol. The anchoring of the antibodies to the micelles was done by using pluronic analog, butylpoly (25) (oxypropylene)poly (20) (oxyethylene) ether of 2-hydroxyacetaldehyde (BPEA). The selectivity and target specificity of the micelles was stamped by Kim et al. (2010) where they used triblock polymeric micelles in murine xenograft model for delivering doxorubicin chemotherapeutic agent to the tumor site. The drug was loaded into the copolymeric micelles that were made of poly (ethylene oxide)-poly [(R)-3-hydroxybutyrate]-poly (ethylene oxide) (PEOePHBePEO) triblock. The activity of the micelles was monitored in monolayer structure of the cell as well as in the 3D multicellular spheroids that successfully resembles the solid tumor site. Mice models with induced tumor were used to study the in vivo effects of the micelles used in the investigation. The study revealed that drug penetration was improved upon the use of micelles that certainly showed that the micelles have a great capability of specific drug delivery. The selectivity of the target site was better than that in case of free doxorubicin. The specific site targeting of the drug through micelles led to effective killing of the affected cells at the diseased site. The drug-loaded micelles also showed minimal toxicity. The ability of the micelles to specifically bind to the target site and hence help in better imaging and diagnosis was shown also by Zhang et al. (2011). The team studied the pharmacokinetic aspect of the annexin A5 by conjugating it with PEG-coated crosslinked polymeric micelles. Fluorescence microscopy and in vitro cell binding studies were performed in order to determine the specificity of the annexin A5-polymeric micelles conjugate. Mice model with induced tumors were used for the experimental study. The study showed strong binding of the annexin A5-micelles conjugates at the targeted apoptotic tumor cell site. The targeted specificity achieved by the micelle–drug conjugate also demonstrated better imaging results from SPECT and fluorescence molecular tomography. The micelle–drug conjugate showed low toxicity and higher uptake as compared to traditional Tc-99 m-labeled HYNIC-annexin A5.

In addition to this, micelles do possess advantageous physical attributes. Their size can be easily controlled by simply varying the hydrophobic block, which is a prominent constituent part of the micelles, and eventually this size range permits for the successful evasion of renal filtration while simultaneously allowing for increased penetration as compared to that of liposomes (Blanco et al. 2009). However, the main limitation with small size, that it limits the amount of drugs that can be successfully incorporated within the core of the micelle (Blanco et al. 2009). Limited drug loading is a serious concern because it leads to faster release of drugs from the micelles, thereby causing premature release prior to the micelle reaching its intended site of action. However, higher drug loading is achieved at the cost of augmented micelle size and aggregation (Blanco et al. 2009). Therefore, chemical conjugation strategies and the strategies for enhancing the biocompatibility of the micelle core with intended drug are being investigated to address the above-mentioned concern.

19.2.7 Dendrimers

Dendrimers have a defined spherical structure which ranges from 1 to 10 nm in diameter (Baker 2009). These are three-dimensional, immensely branched, and well-organized nanoscopic macromolecules possessing low polydispersity index (Madaan et al. 2014). The name dendrimers have been derived from the Greek word dendron that means tree because they have unique tree-like branching architecture (Madaan et al. 2014). They consist of layers between each cascade point that are popularly known as generations. Dendrimers consist of an inner core moiety that is followed by radially attached generations that have chemical functional groups attached at the exterior terminal surface (Madaan et al. 2014). The molecular weight of these macromolecules along with the number of terminal groups tends to increase exponentially as a function of generations (Baker 2009). Based on the core structure that initiates the polymerization process, different types of dendrimers can be synthesized based on the core structure which is responsible for initiating the polymerization process (Baker 2009). Dendrimers can be successfully characterized by a number of techniques like electrospray ionization mass spectroscopy (ES-MS), nuclear magnetic resonance spectroscopy (NMR), high-performance liquid chromatography (HPLC), size exclusion chromatography (SEC) with multi-angle laser light scattering, capillary electrophoresis (CE), and gel permeation chromatography (GPC) (Baker 2009).

Dendrimers are highly soluble in water besides possessing the desirable properties of biocompatibility, polyvalence, and precise molecular weight that clearly makes them a suitable carrier for drug delivery and targeting applications in the clinical operations (Madaan et al. 2014). The dendritic platforms have the potential to be developed into oral delivery systems through the optimization of the size and surface charge. Dendrimers, besides other advantages, also facilitate for the surface functionalization with the help of various targeting moieties such as folic acid (FA), peptides, monoclonal antibodies and sugar groups which helps in achieving the goal of targeted delivery while reducing the toxicity that is involved while employing the conventional methods. The targeted delivery of chemotherapeutics reduces the side effects significantly associated with conventional therapy, where healthy tissues such as liver, spleen, kidneys and bone marrow can accumulate the toxic levels of drug (Madaan et al. 2014). Various studies have been undertaken in order to demonstrate the potential of the dendrimers as highly efficient tools for drug delivery and diagnostics. In one such approach, Kannan et al. (2012) utilized rabbit model for developing and evaluating the performance of dendrimer-based post-natal therapy for targeting neuroinflammation and cerebral palsy. The study revealed that the polyamidoamine dendrimers showed great extent of selectivity and target specificity as they got accumulated and localized in the activated microglia and astrocytes of the newborn rabbits that had cerebral palsy. The team further analyzed the performance of the dendrimers conjugated with *N*-acetyl-L-cysteine (NAC) and found that the resulting therapy was able to suppress neuroinflammation and led to improved motor function in cerebral palsy kits. The study was thus able to stamp the utility of the dendrimers in drug delivery applications. Similar results were obtained in the previous study by Hayder et al. (2011) where the employability of the dendrimers was shown to be fruitful in the fields of drug delivery and medical imaging. The team used mice models for showing the utility of the azabisphosphonate (ABP)-capped dendrimer in the treatment of rheumatoid arthritis. The ABP dendrimer was intravenously injected into the test subjects and was found to be successful in inhibiting and restricting the growth and development of inflammatory arthritis in the test animals. The ABP dendrimer was able to target the site, thereby reducing the levels of inflammatory cytokines. The study concluded that ABP dendrimers can be used as potential treatment tools in the case of rheumatoid arthritis, thereby speaking for the utility of the dendrimers in the field of medical imaging and diagnostics.

19.2.8 Liposomes

Liposomes consist of an aqueous compartment which is surrounded by one or may be more lipid bilayers (Pandey et al. 2016). Liposomes can be classified on the basis of size and number of phospholipid membrane layers (Pandey et al. 2016). Multilamellar vesicles (MLV) are the ones consisting of a number of concentric phospholipid bilayer membranes that are separated by aqueous phase and are big in size, up to 5 µm (Pandey et al. 2016). Small unilamellar vesicles (SUV) have an aqueous compartment which is enclosed by a single lipid bilayer, and their size is in the range of 13–100 nm (Pandey et al. 2016). Large unilamellar vesicles (LUV) consist of single lipid bilayer which surrounds the aqueous compartment and their size lies in the range of 100–240 nm (Pandey et al. 2016).

Liposomes can be used for target-specific delivery and are highly advantageous due to the ability to protect the drug from degradation, thereby reducing the drug-related non-specific toxicity (Pandey et al. 2016). The nature of liposomes is biodegradable, biocompatible, and stable in colloidal solutions. Initially, liposomes were used only for the study of physical behavior of biological membranes like lipids orientation in bilayer, physicochemical characterization of lipids and ion transport across bio-membranes. But in the current scenario, liposomes have found applications in the field of drug delivery as they fulfill all the requirements of being a good drug delivery vehicle (Pandey et al. 2016). There are two methods of drug encapsulation in liposomes—first being the passive loading in which drug is encapsulated during the vesicle formation process and second is the active loading procedure in which the drug is entrapped after the formation of vesicles (Pandey et al. 2016). The loading of hydrophilic drug is loaded within the internal core of the liposomes by mixing them with the hydrating buffer that hydrates the thin lipid film during the formation of liposomes (Pandey et al. 2016) while the lipophilic drug loading is done into lipid bilayers after mixing them with other liposome components during the process of preparation of thin dry film of lipids (Pandey et al. 2016). The method of dialysis or gel-filtration chromatography is often used for removing the un-entrapped drug molecules from the liposome suspension. The encapsulation efficiency depends on number of factors which include lipid concentration, liposome size, and choice of lipids (Pandey et al. 2016). Encapsulation efficiency is found to be comparatively higher for large vesicles while for the water-soluble compounds not interacting with the lipid bilayer; it is found to be relatively low if loading is done by passive method (Pandey et al. 2016).

Liposomes have prolonged systemic circulation which ensures longer interaction of liposomes with the target which is also facilitated by the augmentation of the EPR effect due to greater number of passages of blood through target (Deshpande et al. 2013). Liposomes coated with polymers, such as PEG, are efficiently shielded from reticuloendothelial system (RES) which ensures their longer presence in the blood (Deshpande et al. 2013). PEG coating creates a 'steric stabilization' effect and forms a protective hydrophilic layer on the surface of liposomes that prevents their aggregation and interaction with blood components (Deshpande et al. 2013).

The size of liposomes has been found to have some effects on the passive targeting through EPR effect. EPR effect is utilized in a better way if the liposomes are smaller than 300 nm in size (Deshpande et al. 2013). Although threshold vesicle size of about 300 nm has been reported for extravasation into the affected tissues (Deshpande et al. 2013) More effective and efficient extravasation has been shown to occur with many particles with size less than 116 nm (Mahendra Wijaya et al. 2009).

Loading of the liposomes, with certain weakly acidic or alkaline drug molecules, can be done using active or remote loading method (Pandey et al. 2016). The whole process is governed by the creation of an electrochemical potential through pH, or establishment of ion gradients across the lipid bilayer of liposomes which are created while preparing the liposomes by utilizing the buffer of specified pH and ion concentration (Pandey et al. 2016). Dialysis process is then used for exchanging the external pH of the liposomes by using another buffer of different pH which creates the desired pH gradient across the membranes of the liposomes and then the drug is loaded by mixing it with liposomes at a temperature that is above the phase transition temperature of the lipids to ensure the fluidity across the bilayer. The loaded drug molecules then get charged through interacting with the ions within the liposomes that do not allow them to come out and thus they remain entrapped within liposome core (Pandey et al. 2016). Various studies have been undertaken in order to establish and demonstrate the selectivity and efficacy of the liposomes. Mamot et al. (2004) used rodent models to study the targeted delivery of the liposomes through convection-enhanced delivery system (CED). Directly injected liposomes were loaded with fluorochromes and encapsulated gold particles in order to detect their targeting and localization activity in the central nervous system (CNS). Application of CED led to the efficient distribution of the liposomes in the normal mouse brain. CED-infused liposomes were found to be highly helpful in MRI scans. The labeled liposomes were then infused using CED into the tumor site of the xenograft model, and it was found that the CED-infused liposomes had distributed uniformly across the diseased site that included the hard-to-reach extension into the normal tissues. The team concluded that the CED-infused liposomes can be utilized as a highly efficient tool for imaging and targeting of tumor site. The targeting capabilities of the liposomes were also demonstrated by Song et al. (2008) where they used peptide GE11 conjugated liposomes for targeting epidermal growth factor receptor (EGFR) expressing cancer cells. H1299 xenograft mouse model was used in the study for in vivo analysis. The binding and distribution of the GE11 conjugated liposomes were studied using fluorescence imaging techniques, and it was found that the GE11 conjugated liposomes showed extensive binding and specificity for the EGFR expressing cancer cells. The in vivo analysis demonstrated that the liposomes accumulated at the disease site preferentially and thus helped in achieving better targeting and imaging capacities. De Smet et al. (2011) further stamped the utility of the liposomes as potential drug carriers and contrast agent. The team used rat models for establishing the employability of the temperature-sensitive liposomes (TSLs). The TSLs were encapsulated with doxorubicin and were evaluated using MRI. The in vitro studies showed efficient drug release along with quantitative release of the MRI contrast agent from the lumen of the temperature-sensitive liposomes. The experimental analysis revealed that higher concentration of doxorubicin was recorded due to the combination of hyperthermia and TSLs. This study stamped the drug release of the TSLs as an important tool for monitoring, manipulating, and controlling the drug delivery process.

The actively targeted liposomes, generally, are designed and formulated to minimize off-target effects. These systems are designed and formulated by conjugating targeting moieties on the liposomal surface which enhances their involvement in cellular uptake and thus amplifies the therapeutic response (Deshpande et al. 2013). The amount of drug that is to be delivered to the target cells can be augmented by attaching the liposomes to the vascular cells through non-internalizing epitope which thereby results in the increase in the extracellular drug concentration (Deshpande et al. 2013). The use of receptor-specific ligands or antibodies forms one of the most common strategies, which has been widely explored, to target overexpressed cell surface receptors on infected cells is the use of receptor-specific ligands or antibodies (Deshpande et al. 2013). The prominent types, features, and applications of nanoparticles are also summarized in Table 19.1.

19.3 Surface Functionalization of Nanoparticles

Surface functionalization of nanoparticles provides number of advantages and thus has been extensively explored and monitored, particularly in the fields of biomolecular probing, biological imaging, and drug delivery (Weingart et al. 2013). Since most of the nanoparticles cannot be used alone due to the toxic effects induced by them on the surrounding biological environment, surface functionalization becomes all the more important. Different functional groups/linkers conjugated onto the surface of the nanoparticles, shown below in Fig. 19.2, enable the conjugation of different biomolecules such as antibodies, carbohydrates, peptides, enzymes, aptamer, DNA, etc., to the nanoparticles and thus makes them suitable for many biomedical and clinical applications such as magnetic resonance imaging (MRI), drug delivery, hyperthermia, in vivo monitoring of tumor cell growth, and cell labeling (Weingart et al. 2013). The biomolecules conjugated to the nanoparticles impart various desired properties like specific recognition and biocompatibility (Mout et al. 2012).

Depending on the intended effect, a variety of ligands can be attached to the nanoparticles which allow for the development of either a single function or multimodal capabilities (Weingart et al. 2013). For example, ligands comprising bulky hydrophobic molecules can be attached to the surface of the nanomaterial to prevent agglomeration of the core of nanoparticle, while the surfaces which are used in aqueous environments are coated with water-soluble polymers like poly (ethylene glycol) (PEG) as it enhances solubility and biocompatibility (Weingart et al. 2013). Different polymer coating is highly advantageous because besides providing an alternative to small molecule ligands, they also facilitate for the passive targeting of tumor tissue through the EPR effect (Mout et al. 2012), as shown in Fig. 19.3.

Coating the nanomaterial with PEG and polymers helps in increasing the circulation time and thereby augmenting the probability of particle permeation into affected site, besides preventing the adsorption of blood serum proteins (Mout et al. 2012). Attachment of the targeting moieties on PEGylated nanoparticles has been shown to further enhance the targeting of the nanoparticle (Mout et al. 2012). Ligands provide the flexibility to be attached as “tags” which imparts molecular recognition properties that are highly desirable in drug targeting and bio-imaging applications (Weingart et al. 2013).

Although it is difficult to tailor the nanoparticle interface, however, functionality can easily and efficiently be achieved through synthesis. Due to its intrinsic anti-adhesion properties and specific biological activity across the membrane surface, cell surface membranes have emerged as great models for surface functionalization of nanoparticle, besides facilitating for the construction of an artificial cell

Table 19.1 Various characteristics and brief applications of nanosystems

S. no.	Types of nanoparticles	Size (nm)	Characteristics	Applications	References
1	Quantum dots (QDs)	2–9.5	Semiconducting material synthesized with II–VI and III–V column element; size between 10 and 100 Å; bright fluorescence, narrow emission, broad UV excitation, and high photostability	Long-term multiple color imaging of liver cell; DNA hybridization, immunoassay; receptor-mediated endocytosis; labeling of breast cancer marker HeR 2 surface of cancer cells	Fang et al. (2012), Malik et al. (2013)
2	Superparamagnetic iron oxide nanoparticles (SPIONs)	<100	Biocompatible, very small size resulting in high surface area available for functionalization, stable	Drug and gene delivery, highly sensitive diagnostic assays, thermal ablation and radiotherapy enhancement, contrast agent for MRI	Thomas et al. (2013), Revia and Zhang (2016)
3	Carbon nanotubes (CNTs)	0.5–3 diameter and 13–1000 length	Third allotropic crystalline form of carbon sheets either single layer (single-walled nanotube, SWNT) or multiple layer (multi-walled nanotube, MWNT). These crystals have remarkable strength and unique electrical properties (conducting, semiconducting, or insulating)	Functionalization enhanced solubility, penetration to cell cytoplasm and to nucleus, as carrier for gene delivery, peptide delivery	Liu et al. (2011), Sanginario et al. (2017)
4	Nanoshells	10–116	Favorable optical and chemical properties, spectral tunability	Molecule-specific image contrast, thermal ablation, combined imaging and therapy applications, contrast agent for photonics based imaging modalities	Loo et al. (2004, 2005)

(continued)

Table 19.1 (continued)

S. no.	Types of nanoparticles	Size (nm)	Characteristics	Applications	References
5	Polymer Nanoconjugates	10–1000	Biodegradable, biocompatible, offer complete drug protection	Excellent carrier for controlled and sustained delivery of drugs. Stealth and surface-modified nanoparticles can be used for active and passive delivery of bioactives	Dragojevic et al. (2015)
6	Micelles	10–100	Block amphiphilic copolymer micelles, high drug entrapment, payload, biostability	Long circulatory, target specific active and passive drug delivery, diagnostic value	Oerlemans et al. (2010), Blanco et al. (2009)
7	Dendrimer	<10	Highly branched, nearly monodisperse polymer system produced by controlled polymerization; three main parts core, branch, and surface	Long circulatory, controlled delivery of bioactives, targeted delivery of bioactives to macrophages, liver targeting	Baker (2009), Madaan et al. (2014)
8	Liposomes	40–100	Phospholipid vesicles, biocompatible, versatile, good entrapment efficiency	Long circulatory, offer passive and active delivery of gene, protein and peptide	Pandey et al. (2016), Deshpande et al. (2013)

membrane structure, based on phospholipids, thereby proving effective in the prevention of the non-specific biological reactions at the surface of nanoparticles (Weingart et al. 2013). Different multivalent surface structures that are fabricated with small molecules and polymeric ligands have the capability to facilitate for multiple therapeutic drugs and bio-macromolecules through covalent or non-covalent conjugation (Mout et al. 2012). The ease of such functionalization allows creating the desired functionalities. Along with the conventional metal–thiolate (M–S) linkages, different variety of metal–ligand bonds have also been developed and implied for the functionalization of nanoparticles (Hu et al. 2016). Olefin derivatives have also shown potential to be exploited as new capping ligands for the surface functionalization of nanoparticles. The metal–carbon interfacial

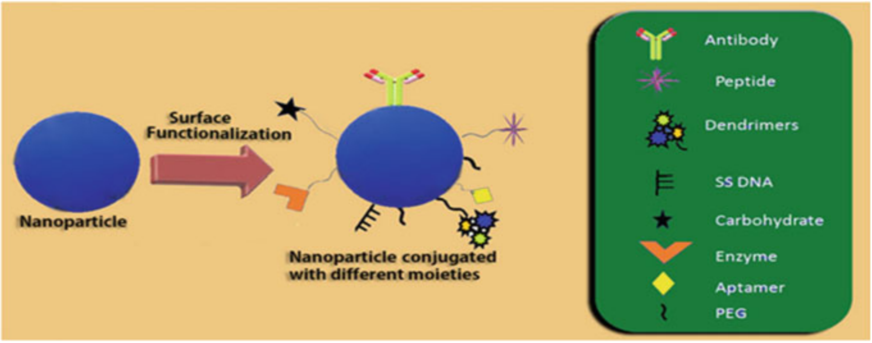

Fig. 19.2 Nanoparticles functionalization with different moieties such as antibody, peptide, dendrimers, ssDNA, carbohydrate, enzyme, aptamer, and PEG. Nanoparticles are attracting huge interest as viable biomedical agents, thus their surface functionalization achieves multifunctional applications

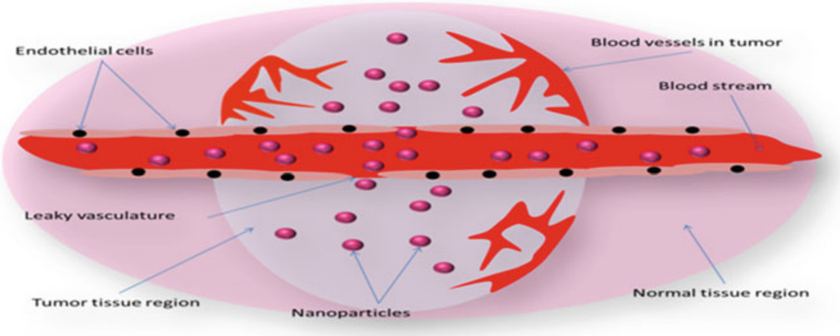

Fig. 19.3 Enhanced permeability and retention (EPR) effect of NPs in tumors. Normal tissue vasculatures are lined by tight, continuous, and well-formed endothelial cells and hence nanoparticles cannot pass the membrane that led to healthy cells. The leaky vasculature in the tumor tissue allows nanoparticles to accumulate in tumor tissue region and thus help in imaging and targeted delivery

bonds have been found to provide the nanoparticles with highly desirable and advantageous optical, electronic, and electrochemical properties because of the effective intraparticle charge delocalization posed by them among the functional moieties and the nanoparticles (Hu et al. 2016).

Surface charge of small molecule coated with nanoparticles dictates their interaction with cell surface molecules and hence their cellular uptake. So, the surface charge along with hydrophobicity and aromatic stacking of nanoparticles has a crucial role in sensing applications (Mout et al. 2012). Also, surface charge has an important role in defining the nanoparticle toxicity because cationic surfaces are more toxic than anionic ones, while the neutral surfaces are the most biocompatible of all (Villanueva et al. 2009). The nanoparticles which are functionalized with positively charged ligands have been found to exhibit higher internalization into cells when compared to the one functionalized with neutral and negatively charged particles (Mout et al. 2012).

19.4 Therapeutic Applications of Nanoparticles

The field of nanotechnology has been developing and advancing throughout which in turn has led to immense development of nanoparticles which has increased their potential application as therapeutic agents, thereby enhancing the targeted drug delivery which is of utmost importance in the clinical and pharmaceutical fields of therapeutics and diagnostics.

Targeted drug delivery using nanoparticles causes improvement in the solubility of drugs which are poorly soluble in water besides enhancing the half-life of the drug systemic circulation by reducing the immunogenicity (Zhang et al. 2008). In the drug delivery system employing the nanoparticles, the administration frequency is low because the drugs are released at a sustained and moderate rate besides being released in an environmentally responsive manner (Zhang et al. 2008). Targeted delivery of drugs helps in minimizing the possible systemic side effects and helps in realizing the task of accomplishing combination therapy by facilitating for the simultaneous delivery of two or more than two drugs which in turn induces a synergistic effect and suppresses drug resistance (Zhang et al. 2008). Owing to these advantages, a number of therapeutic products based on nanoparticles have already been introduced in the pharmaceutical market, while few others are under clinical testing. Liposomal drugs and the polymer–drug conjugates are the dominating classes among these therapeutic agents as they account for about 80% of the total amount (Zhang et al. 2008). Among liposomal drug formulations, Doxil was the first among the liposomal drugs to get an approval by the Food and Drug Administration, USA (FDA) to be used in the treatment of AIDS associated with Kaposi's sarcoma in 1995 (Zhang et al. 2008). Polymer–drug conjugates have also drawn attention to be studied as potential nanoparticle platforms for drug delivery. Small-molecule therapeutic agents have the disadvantage of frequent administration due to short half-life of circulation, moreover, they may lead to undesired systemic side effects due to non-site-specific targeting (Zhang et al. 2008). However, conjugation of these small-molecule drugs to advanced and more efficient polymeric nanocarriers does improve their performance by reducing the unwanted effects. Polymer–drug conjugates are helpful in increasing the in vivo circulation time besides reducing the cellular uptake to the endocytic route (Zhang et al. 2008), which in turn enhances the passive drug delivery to the tissues that consist of leaky vasculature, such as tumors and atherosclerotic plaques (Zhang et al. 2008). Even though a lot of polymeric conjugates have been proposed, only a few have been able to make a mark in the clinical practice as drug carriers. PEG is one of the most preferred ones as it has the potential to augment the plasma stability and solubility of the drug besides reducing its immunogenicity (Zhang et al. 2008). Linear polymers such as polyglutamic acid, polysaccharide, and poly(allylamine hydrochloride) have also made way for themselves in the clinical practice of being used as potential polymeric drug delivery carriers (Zhang et al. 2008). Polymeric micelles, apart from liposomes and polymeric conjugates, have also drawn considerable attention as drug delivery nanocarriers owing to their remarkable therapeutic potential (Zhang et al. 2008). The hydrophobic core present in the micelles can carry pharmaceuticals, especially the drugs which have poor solubility, with superior loading capacity (5–25 wt%) (Zhang et al. 2008), while the hydrophilic shell present in the micelles does the important job of providing steric protection which thereby increases the stability in blood besides facilitating for various functional groups that are suitable for further modification (Zhang et al. 2008). Polymeric micelles have the capability to carry more drugs due to their considerably large size and have the capability to co-deliver two or more drugs that are having similar or may be even different water solubility for combination therapy (Zhang et al. 2008). External factors such as change in pH and temperature are also sometimes responsible for the release of drugs from polymeric micelles (Zhang et al. 2008). They are more stable in blood when compared to liposomes as they show lower value of critical micelle concentration (Zhang et al. 2008). The capability for the simultaneous delivery of two or more therapeutic modalities such as radiation agents and drugs is another advantage of polymeric micelles (Zhang et al. 2008). Surface modification of these micelles by peptides, antibodies, aptamers, carbohydrates, nucleic acids, etc., increases their specificity and efficacy besides reducing their systemic toxicity (Zhang et al. 2008). Dendrimers find themselves in the novel class of drug delivery nanoparticle platforms because of their well-defined architecture and unique features (Zhang et al. 2008). Dendrimers have multivalent surfaces on which they can carry drugs by using covalent conjugation or electrostatic adsorption (Zhang et al. 2008). Cavities of dendrimers in their core can be utilized for drug loading based on the principles of hydrophobic interaction and hydrogen bonding (Zhang et al. 2008).

The novel properties of nanoparticles are due to their unique size, wide variation in the shape, and the ease of their surface to be functionalized which ensures specific drug delivery and conjugation of specific biomolecules on the surface that helps in overcoming numerous biological barriers (Rodzinski et al. 2016). Targeted nanoparticles deliver chemotherapeutic agents passively or actively which thereby enhances the intracellular concentration of drugs/genes in the cancer cells while avoiding toxicity in normal cells (Nguyen 2011). In addition, the targeted nanoparticles, besides other advantages, have the ability to be designed as pH-sensitive and/or temperature-sensitive carriers which adds up to the flexibility of their application (Nguyen 2011). The pH-sensitive drug delivery system delivers and releases the drugs within highly acidic microenvironment of the diseased cells and/or components within them (Nguyen 2011). The temperature-sensitive system has the potential to carry and release the drugs with temperature changes happening locally in the affected region which is ensured by the sources like magnetic fields, ultrasound waves that further enhances the efficiency of the procedure (Nguyen 2011). Use of specific features/moieties for the targeting of nanoparticles to diseased site minimizes the possible effects of composition, size, and molecular mass of nanoparticles on their efficacy. The toxicity of the targeted nanoparticles can be further reduced by simple modifications or functionalization in their surface chemistry (Nguyen 2011).

Although targeted nanoparticles overcome the problem of lack of specificity in conventional chemotherapy, there are certain potential risks and challenges which are associated with this novel strategy that needs immediate attention. One of the major problems being the possibility of some diseased cell types developing drug resistance over the treatment course which could possibly render the drugs released as ineffective which would certainly not help the cause (Nguyen 2011). However, this problem of drug resistance can be sorted out by the use of targeted nanoparticles for the delivery of both chemotherapeutics and gene therapeutics, which would increase the specificity. Multifunctional targeted nanoparticles are another strategy which can help to overcome the problem of drug resistance (Nguyen 2011). The problem of premature drug release in the plasma or interstitial space rather than at the intended site, however, remains, despite the great potential shown by the nanoparticle drug delivery (NDD) systems. However, this problem has been addressed by formulating nanoparticles to allow for triggering drug release by external factors like applied temperature, ultrasound waves, intracellular pH, or the intracellular enzymes (Rodzinski et al. 2016). Still, these approaches suffer from the discrepancy of inconsistent drug release and thus use of nanoparticle drug delivery (NDD) systems to control retention and specific delivery of the drug remains a major open question (Zhang et al. 2008).

19.4.1 Applications of Nanoparticles in Biomarker Detection

Significant improvement has been made in the development of sensitive, robust, and versatile platforms that are to be used for early detection of diseases by the use of various biomarkers. A biomarker is a biological molecule that is found in blood or even in other body fluids and tissues and reflects the state of a process, whether it is normal or abnormal (Bohunicky and Mousa 2011). They are probably the most valuable tool that can be employed for early detection of the disease, accurate pretreatment staging, determination of the response shown by the disease or the abnormality to the applied chemotherapeutic treatment and monitoring the progression of the disease (Bohunicky and Mousa 2011). Biomarkers are found not only in body fluids such as blood, serum, urine (Gandhi et al. 2009), or the cerebral spinal fluid (CSF), but also in or on diseased cells which thereby paves the path for their wide application in the field of detection and imaging (Bohunicky and Mousa 2011). These biomarkers need to be diagnosed as they are expressed at early onset

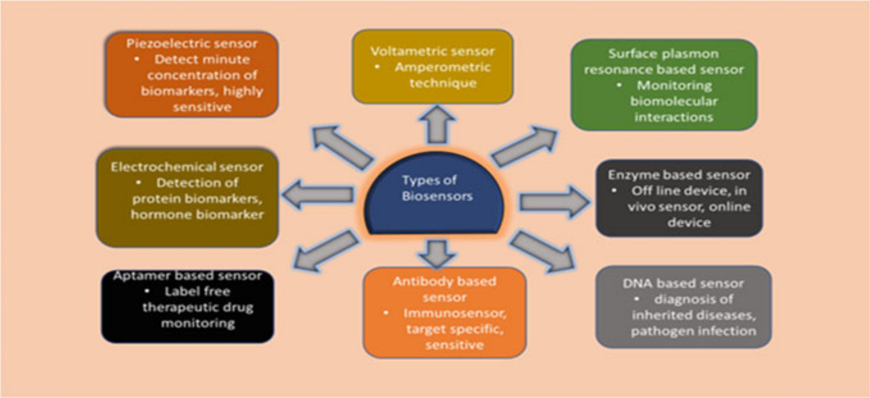

Fig. 19.4 Schematic representation of the various types of biosensors. They are emerging as indispensable tools with widespread applications in the biomedical field

of disease. A device which is used to detect these biomarkers, which can be environmental or biological in nature, is called a biosensor (Bohunicky and Mousa 2011). Biosensors use the change in the level of certain proteins which are expressed by the affected cells as the indicator to detect and analyze about the presence of any disease and the efficiency of the treatment being carried out (Bohunicky and Mousa 2011). Biosensors also have the capability to detect multiple analytes and such sensing devices prove highly useful in diagnosis and monitoring because it saves not only time but also financial resources.

Different types of biosensors such as electrochemical, voltammetric, piezoelectric, surface plasmon resonance (SPR), enzyme, antibody, aptamer, and DNA-based sensors have been developed using antibody, DNA, aptamer, enzymes, proteins, etc. Figure 19.4 gives examples of various biosensors developed so far, for the detection of multiple biological analytes.

19.4.1.1 Electrochemical Sensors

Electrochemical sensors are miniaturized devices that work in conjugation with different NPs and offer enhanced sensitivity and selectivity. Conventional approaches have used the sandwich immunoassay as their workhorse method for detection (Rusling et al. 2013), however, electrochemical sensors have put themselves forward as a better alternative for detection owing to their high specificity and suitability for onsite analysis (Suman et al. 2017). An electrochemical sensor possesses the potential to detect varied targets like embryonic antigen, carbohydrate antigens, enzyme and isozyme, proteins, and hormones (Chandra 2015). Although classic ELISA approach is the most widely accepted and preferred for high sensitivity applications, it has certain limitations in the context of analysis time, sample size, equipment cost, and measurement of the collections of proteins (Rusling et al.

2013). The immunoassay principle has long been used for the monitoring and detection purposes (Wijaya et al. 2010) with one being pioneered specifically for electrochemical immunoassays where sandwich-type immunoassays used the enzyme label alkaline phosphatase that successfully produced various electroactive products that were eventually transported by a chromatographic or fluidic system to an electrode detector (Rusling et al. 2013). Microfluidic devices also use the very same concept which has been studied in recent studies. The concept of conjugation of antibodies to the sensor surface, which eventually facilitates for the capture of analyte, has also been explored for the development of self-contained single analyte electrochemical immunosensor (Rusling et al. 2013).

Multiplex detection strategies which include the integration of electrochemical sensors with microfluidic system has also drawn interest as they are capable of the simultaneous detection of disease markers (Chandra 2015). One of the examples of integrated microfluidic system is the detection of breast cancer markers through electrochemical methods directly in the serum samples of the patient (Chandra 2015). The results were found to be in good correlation with that of the conventional ELISA method that clearly reflects the huge potential of the microfluidic integrated electrochemical sensor that was used for multiplex detection of biomarkers (Chandra 2015). Chikkaveeraiah et al. (2011) also utilized the microfluidics integrated electrochemical immunoassay system for the simultaneous detection of interleukin-6 (IL-6) and prostate-specific antigen (PSA). The team used a channel of molded poly-dimethyl siloxane. That channel was interfaced with a pump and test sample injector. An offline recognition of the target compounds was done by employing the bio-conjugate of enzyme-labeled superparamagnetic particle and antibody. After being captured, the antibodies were attached to a chip consisting of eight-electrode for the measurement purpose. The developed system was able to detect the biomarkers with low detection limit in and high sensitivity. Schematic representation of ELISA is shown below in Fig. 19.5.

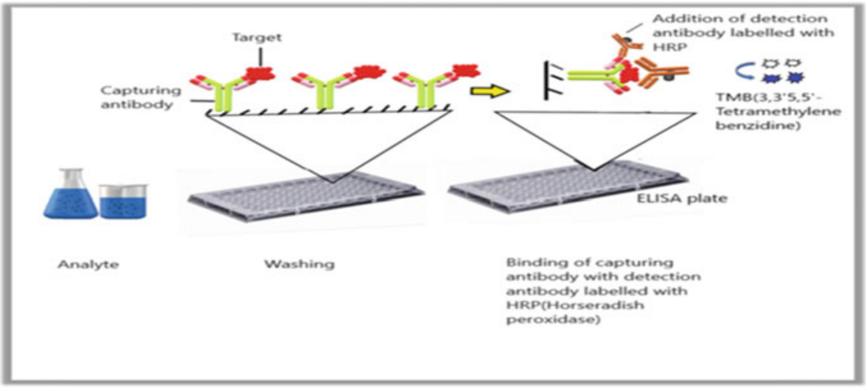

Fig. 19.5 Schematic representation of enzyme-linked immunosorbent assay (ELISA). It deals with the utilization of antibodies and color change to identify a substance and is a highly sensitive procedure to quantify the concentration of an antibody or antigen in an unknown sample

19.4.1.2 Voltammetric Sensors

Voltammetry is a part of the bigger domain of electro-analytical methods (Grieshaber et al. 2008). It is an amperometric technique because the analyte information is obtained and determined by applying variable potential and then measuring the resultant current. Since there are numerous ways to vary a potential, it is no surprise that many forms of voltammetry exist such as: polarography (DC Voltage), linear sweep, differential staircase, normal pulse, reverse pulse, and differential pulse (Grieshaber et al. 2008). In cyclic voltammetry (CV), the voltage is estimated between the reference and the working electrode, while the current is, however, gauged between the working and the counter electrode. CV is widely used because it is very useful in obtaining relevant information about the redox potential and electrochemical reaction rates related to the analyte solutions (Grieshaber et al. 2008). The obtained data is plotted as current versus voltage, which, is known as voltammogram. Its shape, for a given compound, depends on the scan rate as well as the electrode surface, which, however, is different after each adsorption step but may even depend on the concentration of the catalyst (Grieshaber et al. 2008).

19.4.1.3 Piezoelectric Sensors

High sensitivity and quick response time are the advantageous attributes of piezoelectric sensors. These sensors depend upon the change in mass on the surface of the sensor (Griffin 2017). A piezoelectric (PZ) sensor is capable of interpreting small changes in frequency, mass or any other tangible property of the bio-recognition element. Most piezoelectric sensors obtain their highly advantageous characteristics because of the inherent signal transduction system (Griffin 2017). In these sensors, immobilization of an antibody is realized on the sensor surface, the change in mass of which facilitates for the detection of change in the frequency when the binding occurs (Griffin 2017). Analyte determination is completed by the measurement of the oscillation frequencies (Pohanka 2017). The mass bound to the crystal surface slows down the oscillations, and the direct relationship between the bound mass and the frequency shift for common quartz crystal was described by following formula (Sauerbrey 1959):

$$\Delta f = \left(-2.3 \times 10^{-6}\right)\left(f_{\mathrm{o}}^{2}\right)(\Delta m/A)$$

where,

f_{o} fundamental mode of the crystal oscillation in hertz and
A piezoelectrically active area in centimeters.

The Sauerbrey equation is reliable for a rigid, thin-film attached to the electrode surface but when ambient environment is not unchanged, equation described by (Kanazawa and Gordon 1985) for quartz crystal should be taken into consideration, which is as follows.

$$\Delta f = \{(f_o)^{3/2}\}\{(\Delta(\rho_1 \cdot \mu_1))/(\pi \cdot \rho_q \cdot \mu_q)\}^{1/2}$$

where,

ρ_l	density of ambient liquid in g/cm^3
μ_l	viscosity of ambient liquid in centipoise
ρ_q	density of quartz in g/cm^3
μ_q	viscosity for quartz crystal in centipoise.

Pohanka and Skládal (2008) developed a sensitive piezoelectric sensor for the determination and quantification of whole bacterial cells. Polyclonal antibodies were used against *Francisella tularensis* by immunizing white BALB/c mice. The immobilization of antibodies was done on the surface of 10 MHz quartz crystal microbalance (QCM). The biosensor was found to work well but the frequency change caused by the interaction between antigen–antibody and bacterium was found to be low. Pohanka and Skladal (2007) used the experimental setup very close to one mentioned above for the label-free determination of tularemia. In this study, the immobilization of the antigen was done onto the surface of QCM and the antibodies were successfully assayed as diagnostic markers. Serum samples were used for the analysis of the sensor performance and the results showed excellent oscillation changes. The performance of the sensing device was found to be well correlated with that of the standard enzyme-linked immunosorbent assay.

19.4.1.4 Surface Plasmon Resonance (SPR)-Based Sensors

There are various optical sensing methodologies available but surface plasmon resonance (SPR)-based systems are rated high because of their high sensitivity and the ability to provide an efficient method for label-free detection and monitoring of biomolecular interactions in real time (Wang et al. 2016). This technique is based on the measurement of the change in the refractive index in the proximity of thin metal layers (i.e., gold, silver, or aluminum films) (Nguyen et al. 2015). Capturing agents such as antibodies, enzymes, peptides, and DNAs are used and immobilized onto the surface prior to the flow of the sample solution across the SPR surface. The change in the angle of minimum reflectivity, which is also called the SPR angle, is measured and determined by causing variation in the incidence angle and thereby recording the intensity of the reflected light while the reactions including biological binding are in progress between various biomolecules (Nguyen et al. 2015). The defined SPR angle, at which the condition of resonance occurs, depends upon the refractive index of the material near the thin metal surface under the influence of constant light source (Nguyen et al. 2015). Consequently, when there is a small change in the refractive index of the sensing medium (e.g., through biomolecule attachment), plasmon, however, cannot be formed when there is very small change in the reflective index of the sensing medium and hence in such conditions, the detection is carried out by measuring the changes in the reflected light which is obtained on the detector (Nguyen et al. 2015).

Resonance or response units (RU) are used as the unit to describe and define the signal change in the SPR experiments. 1 RU is equivalent to a shift in critical angle by about 10^{-4} degrees (Nguyen et al. 2015). Prior to the commencement of probe–target interactions, the initial RU value corresponds to the critical angle value recorded in the starting. The change in refractive index Δn_{d} which arises within a layer of thickness h can be calculated by the following relation:

$$\Delta n_{\mathrm{d}} = (\mathrm{d}n/\mathrm{d}c)_{\mathrm{vol}}\, \Delta\Gamma/\mathrm{h}$$

where $(\mathrm{d}n/\mathrm{d}c)_{\mathrm{vol}}$ is the increase in refractive index, n, with the volume concentration of analyte c, and $\Delta\Gamma$ is the concentration of the bound target on the surface (Nguyen et al. 2015). The change in the refractive index is monitored by coupling the incident light into a propagating surface plasmon (PSP) on the gold surface in real time (Nguyen et al. 2015).

An SPR biosensor generally has the limit of detection of the order of 10 pg/mL, however, the detection limit in SPR experiment may depend on a number of factors that include molecular weight, optical property and the binding affinity of the target-probe molecules (Nguyen et al. 2015).

The development of a multichannel SPR-based biosensor which was intended to accurately and simultaneously detect AFP (α-fetoprotein), CEA (carcinoembryonic antigen), and CYFRA 21-1 (cytokeratin fragment 21-1) has been reported in a recent study (Wang et al. 2016). The sensitivity of detection of the sensor was improved when dual signal amplification strategy was used by employing AuNPs-antibody conjugates and antibody-QD (quantum dots) conjugates. Formation of AuNPs monolayer as an active interface over the chip surface using Hexanedithiol (HDT) as a chemical linker greatly improved the sensitivity of the sensor. The results highlighted an improvement in the detection limit (LOD) which was primarily because of the enhancement in the signal that was caused by adding the antibody-QD conjugates. The sensor showed negligible non-specific binding of detection and was found to be highly selective for AFP as no effect was recorded to be caused by the presence of other contaminating proteins which could have been possible present in the serum samples.

19.4.1.5 Amperometric Sensors

Amperometric biosensors are based on the production of current while a fixed potential is applied between two electrodes under application. These sensors are quite easy to miniaturize while being simultaneously robust and have the advantage of being able to operate with very small sample volumes of even complex matrices (Rocchitta et al. 2016). The enzyme-based amperometric biosensors could be used in the following ways, (Rocchitta et al. 2016):

i. As off-line devices—in which the biological samples are accumulated, and the target analytes are measured through the biosensor-based analytical equipment.
ii. As in vivo sensors—in which the implanted biosensor continuously detects the extracellular changes in the analyte concentration. Since these are invasive in nature, their use is limited to preclinical research in animal models.
iii. As online device—in which a sampling device is integrated along with the biosensor and is then implanted in the body or the biological environment.

Amperometric enzyme biosensors are divided into three main classes or generations, and the division is dependent upon the electron transfer method which is used for the measurement of the biochemical reaction and the degree of separation within the biosensor components (Rocchitta et al. 2016). The presence of an enzyme is common in all the classes and therefore the performance of the sensor relies on different parameters, such as the working pH and temperature (Rocchitta et al. 2016).

First-generation biosensors are characterized by the generation of an electrical response after measuring the concentration of analytes and/or products formed in the enzymatic reactions which get diffused to the surface of the transducer and due to this reason, these sensors are also called as the mediator-less amperometric biosensors (Rocchitta et al. 2016). These biosensors exploit the capability of a substrate to get transformed into an electroactive and measurable byproduct by the immobilization of the enzyme onto the surface of the transducer (Rocchitta et al. 2016). Such type of biosensors relies on enzymes that primarily belong to two broad categories: oxidases and dehydrogenases (Rocchitta et al. 2016). First-generation biosensors are characterized by high sensitiveness and low-response times which are typical of the order of around one second (Rocchitta et al. 2016). However, first generation biosensors suffer from some limitations like the requirement of electrode pretreatment to generate reproducible surface and sensor response, and the necessity of the corrections for matrix effect which are related to interference (Rocchitta et al. 2016).

Second-generation biosensors are called as mediator amperometric biosensors because they employ mediators such as oxidizing agents which act as the electron carriers (Rocchitta et al. 2016). These sensors can work at low potentials and have the capability to avoid O_2 dependence and the impact of interfering molecules (Rocchitta et al. 2016). Ferricyanide and ferrocene are most preferred, however, other options like methylene blue, phenazines, methyl violet, alizarin yellow, and Prussian blue are also widely used (Rocchitta et al. 2016). Second-generation biosensors have limited application due to their lower stability (Rocchitta et al. 2016).

Third-generation biosensors are based on the principle of bio-electrocatalysis and involve the direct transfer of electrons between enzyme and electrode (Rocchitta et al. 2016). Third-generation biosensor consists of three main elements, namely: the enzyme which acts as the biorecognition element, the redox polymer which ensures the propagation of the signal and the electrode which is utilized as the surface for entrapment (Rocchitta et al. 2016). Third-generation biosensors are still in development phase and hence are not used in common (Rocchitta et al. 2016).

19.4.1.6 Antibody-Based Sensors

Antibodies (Abs) find a pivotal role to play in several sensors owing to their exquisite target specificity and affinity and hence, find themselves among the most widely designed and engineered molecules used as diagnostic tools (Sharma et al. 2016). The performance of any immunosensor depends upon the type of Ab and the associated approach of Ab-immobilization (Sharma et al. 2016). The preparation of Ab in antiserum against a specific target, using the conventional techniques, consistently results in the production of non-homogeneous Abs, also referred to as polyclonal Ab (pAbs). They encounter the problem of variable specificity and affinity which is, however, successfully countered by the monoclonal Ab (mAb) technology or the hybridoma technology which in turn has revolutionized the utilization of Ab as a tool for research in the prevention, detection, and treatment of diseases (Sharma et al. 2016).

There are three vital factors that affect the performance of a bio/immuno-sensor: (i) ability to immobilize recognition elements (biological molecules) while simultaneously maintaining their inherent natural activity; (ii) accessibility of the recognition element to the analyte of interest in the solution; and lastly, (iii) low non-specific adsorption to the solid support (Sharma et al. 2016). Limiting the non-specific adsorption and optimal immobilization of the Abs without causing change in the specificity and immunological activity of the sensor forms one of the most crucial steps in the fabrication of an immunosensor which depends largely on the physicochemical properties of the sensor surface (Sharma et al. 2016). Since immunosensors provide the desired output with good precision and low detection limit (Thakur et al. 2011), they are employed not only for the detection and monitoring of disease markers but also for some environmental pollutants which indirectly affect the animal health (Suri et al. 2008). (Ionescu et al. 2010) designed and developed a sensitive label-free impedimetric immunosensor and used it for the detection of atrazine. Detection was done by immobilization of the anti-atrazine Ab fragments which was done by using the affinity binding on a polypyrrole film. This film was *N*-substituted by nitrilotriacetic acid (NTA) electrogenerated on a gold electrode. The immunosensor was reported to show high sensitivity with detection limit as low as 10 pg/ml with a working linear range of 10 pg/ml to 1 μg/ml. A fusion protein, specifically the Protein A–gold-binding domain (PAG) was developed, to develop a fast and oriented Ab-immobilization approach (Sharma et al. 2016). The immunosensor showed high sensitivity with a limit of detection earmarked at 90 ng/ml and the inter-chip variability was found to be lower than 7%.

19.4.1.7 Aptamer-Based Sensors

Label-free therapeutic drug monitoring (TDM) has successfully led to the development and implementation of personalized point-of-care (POC) therapy applications by utilizing the potential of electrochemical and field-effect biosensors, and this has eventually made them of great interest in the last decade (Aliakbarinodehi et al. 2017). Electrochemical and field-effect biosensors have a definite edge over the traditional optical techniques for TDM in the context of factors like availability, cost-effectiveness, simplicity, and portability (Aliakbarinodehi et al. 2017). Aptamers, being short oligonucleotide sequences and ability to show specific conformational changes, have the capacity to strongly bind to their targets with high degree of affinity and specificity (Aliakbarinodehi et al. 2017). Aptamers have several advantages over antibodies like the ease of synthesis and modification, stability in long term, and high specificity, which makes these biomolecules a preferable option for the development of desired analytical devices (Sharma et al. 2012). Aptamers, besides being chemically stable, have the property of retaining most of their functionality even after the realization of multiple regeneration steps (Aliakbarinodehi et al. 2017).

Aptamers have specific edge over antibodies because they have high selectivity even for the targets that are not easily recognizable to antibodies (e.g., ions, small molecules, etc.) (Kumar 2017). Aptamers, possess a number of definite advantages as biorecognition element, over antibodies and enzymes which includes the ease of chemical modification, structural flexibility along with conformational flexibility, high pH stability and reversible thermal denaturation (Kumar 2017). Studies concerned with the fabrication of aptamer-based biosensors have shown and proved that aptamer probes exhibit high affinity besides being highly specific toward their respective targets (Sharma et al. 2012).

Immunosensing platforms are known to provide high sensitivity (Gandhi et al. 2018b) when compared to the conventional assays as aptamer-based ELISA and other novel immunosensing strategies have already been found to be more reproducible, robust, and economical (Kumar 2017). Not only for the detection of small molecules lacking enough epitopic determinants, but aptamers have the capacity to be highly selective even when antibodies can be cross-reactive in a situation where two molecules are same but at a single functional position (Kumar 2017).

It has been reported that a biosensor can be utilized for the monitoring of the targeted drug tenofovir (TFV) (Aliakbarinodehi et al. 2017). Principle of surface plasmon resonance (SPR) was employed to measure the response of the sensor against the specific and non-specific drug—aptamer interaction at different buffer conditions. The optimization of the biosensing interface was done by using the electrochemical impedance spectroscopy (EIS) in which, best ratio between thiolated aptamer and MCH (6-mercapto-1-hexanol) concentrations used in the immobilization process was found out. The AptaFET biosensor was used for obtaining the dose-response behavior of the system. The calculated limit of the detection for the AptaFET was found to be lower than the usual electrochemical sensors.

19.4.1.8 DNA-Based Sensors

Nucleic acid recognition processes form the basis of DNA-based nanosensors which are unarguably the most prospective type of nanosensors and thus are being rapidly used for the development of assays for simple and efficient testing of genetic material and infectious agents (Abu-Salah et al. 2015). They are fabricated and developed by immobilization of single-stranded probes on different electrodes using electroactive indicators, which measure the hybridization between DNA strands and their respective complementary DNA probes (Abu-Salah et al. 2015). Detection of specific DNA sequences is highly important not only in the field of clinical diagnostics but also in the area concerning environment assessment and food analysis (Abu-Salah et al. 2015) and due to this only, DNA is highly preferred as a sensing tool as compared to other available nucleic-acid-based probes (Bora et al. 2013). Bioreceptors help in the development of highly sensitive techniques which can be employed for detection purpose (Suri et al. 2009). Nucleic-acid-based biosensors (NABs) primarily maneuvre, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), peptide nucleic acid (PNA), and aptamers (both DNA and RNA) as oligonucleotide probes and enjoy wide domain of applications in the respective fields of (i) clinical diagnostics applied for the inherited diseases and pathogenic infections, (ii) laboratory analysis, like one involved in the development of probe for different hybridization techniques as well as microarray systems (Bora et al. 2013). The Chargaff's rules of base pairing form the fundamental underlying principle behind NABs, the only exception being the aptamers (Bora et al. 2013).

DNA-based nanobiosensors are better option when compared to the conventional hybridization techniques, including the gene chips because they facilitate for the detection of disease and help in obtaining sequence-specific information in much faster, simpler, and cost-effective manner. The regeneration capability of the nucleic acid recognition layers in DNA-based nanobiosensors, which makes them suitable for multiple uses, is not found in enzymes or the antibodies (Abu-Salah et al. 2015).

DNA-based probes facilitate for the augmentation of the signal generated by the biosensor by making sure the amplification of a desired target DNA from the host–pathogen by the use of PCR (Bora et al. 2013). The synthesizable biological recognition layers formed and sustained by the DNA are usually very stable along with being reusable even after DNA duplex melts down through thermal process, which is, however, not the case with enzymes or the antibodies (Bora et al. 2013).

19.4.2 Application of Nanoparticles in Imaging

Imaging modalities in the present scenario include MRI (shown in Fig. 19.6), CT, photoacoustic imaging (PAI) and ultrasound, optical imaging (OI), as well as positron emission tomography (PET) and single-photon emission CT (SPECT) and since these are based on different underlying physical principle, therefore, each of

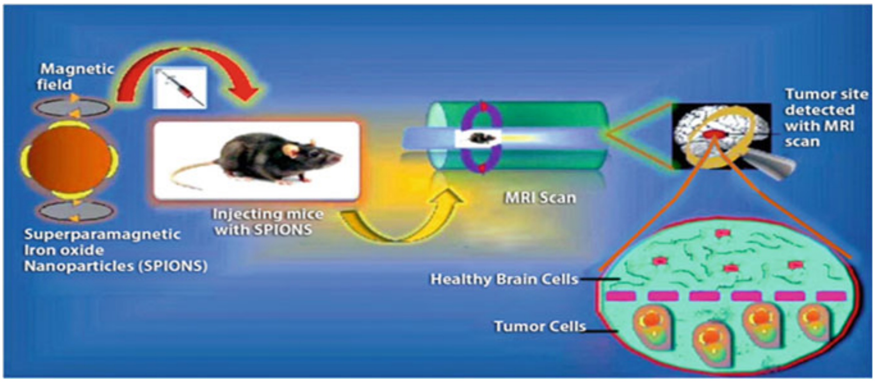

Fig. 19.6 Imaging of brain tumor in mice using MRI. A large external magnetic field aligns the magnetic moment of the sample protons and contrast agent protons. SPIONS are the preferred contrast agents, over Gadolinium, due to their better physicochemical properties and higher relativity. MRI has been adapted for screening and detecting brain tumors in mice based upon their imaging characteristics appearance and their pattern of enhancement. The imaging characteristics of the tumors could potentially be used as one criterion of efficacy for strategies being developed and tested

them offer specific advantages and disadvantages in the context of sensitivity and specificity to contrast agents and other factor like tissue contrast, spatial resolution, quantitative and tissue penetration (Baetke et al. 2015). Nanoparticles like the polymers, liposomes, ultra-small superparamagnetic iron oxide (USPIO) nanoparticles and gold nanoparticles have the potential to be used as contrast agents for functional as well as molecular imaging (Baetke et al. 2015; Gandhi et al. 2018a).

19.5 Hyperthermia-Based Therapy

Hyperthermia can be defined as a rise in the temperature of the body tissues which may be global or local. When the temperature gets elevated high enough to cause or initiate immediate cellular death, predominantly through necrosis assisted by irreparable coagulation of proteins and other essential biological macromolecules, then it is termed as thermoablation. Hyperthermia, on the contrary, refers to smaller elevations in temperature levels which usually falls in the range of 30–35 °C and is sufficient to initiate a series of subcellular events which eventually renders the cells vulnerable to various forms of damage which include apoptosis, ultimately leading to cell death. Other effects are also highly likely which may include the activation of immunological responses, augmentation of tumor blood flow and oxygenation through greater vascular permeability and perfusion, or a shift toward anaerobic metabolism which ultimately results in decreased oxygen consumption and enhanced tissue oxygenation, all of that leading to an altered extracellular microenvironment which helps in killing the affected cells (Mallory et al. 2016).

Three categories of hyperthermia are conventionally employed in clinical practice, namely—whole-body, regional, and local. While the whole-body hyperthermia is achieved by methods such as hot-water blankets and thermal chambers and is applied for diseases with metastatic nature where the local hyperthermia proves to be ineffective. Regional hyperthermia, however, depends on the method of perfusion with heated liquids for which the two popular techniques are: perfusion of peritoneum with the heated solution containing drugs, and second is perfusing a part of the patient's blood, taken out and warmed ex vivo, into an artery which is supplying the blood to the limb containing the disease (Kok et al. 2015). Both above-mentioned types of hyperthermia result in poor specificity of treatment and hence are not very advantageous in general sense. Even though the toxic effects of hyperthermia are usually not severe, whole-body hyperthermia involves greater risk as it often leads to the onset of complexities like gastrointestinal symptoms, diarrhea, nausea, and vomiting and may also occasionally make way to seriously dangerous cardiovascular side effects which may include myocardial ischemia, thrombosis, and cardiac failure. The underlying problem with regional hyperthermia, which restricts its applications, is its invasive nature and involvement of significant challenges in the setup. Local hyperthermia, on the other hand, in theory, has the advantage of being focused and concentrated. Three major methods of generation of local hyperthermia are generally discussed in literature, which, in order of their increasing invasiveness, are external, luminal, and interstitial (Kaur et al. 2016). The luminal hyperthermia employs special probes which are placed very close to the affected site, while in interstitial hyperthermia there is a use of a grid of applicators or probes that are placed into the parenchyma in order to achieve more uniform heating of the affected site. For the heating purpose, the heat sources can either be inserted into the probes, or the probes themselves can be heated by the application of some suitable external heating source. These methods generally suffer from high degree of invasiveness, with the heating produced at the affected site still being nonuniform owing to the fact that it is concentrated more on the probe rather than elsewhere. However, placing metal antennas and getting them heated up in the influence of an alternating electromagnetic field, within the interstitium of affected site prior to the exposure to any external magnetic field is a simple and successful way to achieve higher degree of uniform heating as in this way, the heat required for hyperthermia is generated inside the tumor site rather than being filtered in from outside, and thus is easily controllable by simply putting a control over the strength of the applied magnetic field (Haik and Chen 2010). The study with magnetic heating of iron oxide nanoparticles and demonstrated successfully that hyperthermia can be achieved by applying an external excitation in the form of an alternating magnetic field and the in vivo experiments were completed employing the mouse xenograft models which showed in the results that the temperature at tumor center got elevated quickly so as to cause hyperthermia-mediated cell death through oncotic necrosis (Zhao et al. 2012). Since electromagnetic radiation and high-intensity focused ultrasound waves, both, have the potential to transduce energy from an external source to pass through the body, they both present an option to be used as a tool for achieving external heating. However, one of the most undesired disadvantages of this method is the deposition of energy in the normal tissues lying along its path which ultimately results in the formation of hot spots within these tissues.

Advances in nanoscale materials have not only helped in the development of highly sensitive immunosensors for drug detection (Gandhi et al. 2015) but have also provided a potential non-invasive means of heating cells to therapeutic (i.e., cytotoxic) levels owing to the fact that the molecularly labeled nanoparticles allow for the non-invasive implementation by using non-ionizing electromagnetic radiation and thus puts forth a better option (Chatterjee et al. 2011). Nanoscale metallic particles having the potential to convert the electromagnetic energy into heat can readily be used for achieving the goal of targeted hyperthermia (Chatterjee et al. 2011). The electromagnetic heating of nanoparticles for the treatment does present tremendous opportunities on one hand while forwarding some challenges on the other, especially for the non-invasive method and treatment of temperature-sensitive diseases. Nanoparticles like the iron-oxide nanoparticles (IONPs), gold-based nanoparticles (AuNPs), and carbon-based nanoparticles (CNPs) have successfully been tested for the task of localized heat generation upon exposure to the external excitation or energy fields (Cherukuri et al. 2010). Iron oxide nanoparticles have proved themselves to be highly advantageous and versatile as they have been used as both diagnostic and therapeutic nanoscale materials which have immense potential to treat deep tissue disease like tumors (Chatterjee et al. 2011). Size-dependent mechanisms generate heat when magnetic nanoparticles such as iron-oxide nanoparticles are subjected to external oscillating magnetic fields. This phenomenon has been shown in Fig. 19.7.

Gold nanoparticles are solid gold nanospheres with diameter range from 2 nm to several 100 nm and exhibit characteristic extinction spectra as a result of plasmonic absorptions (Chatterjee et al. 2011). Recently, advancements have been made in the production of gold–silica nanoshells that are composite nanoparticles comprising of an inner silica (glassy) core diameter with a thin outer layer of gold and are capable of producing redshift in gold's characteristic plasmon absorption spectrum into the near-infrared (NIR) region (640–940 nm) (Chatterjee et al. 2011). The NIR absorptions have the capability to heat nanoshells within the diseased cells and thus have proved to be efficacious in the treatment of superficial tumors (Chatterjee et al. 2011). Although, NIR photothermal therapy can be used for the treatment of superficial tumors but not for the treatment of deeper organ-based diseases because NIR light is significantly attenuated by the cellular matrix of the body (Chatterjee et al. 2011).

Single-walled carbon nanotubes (SWNTs) consist of an one-dimensional structure which comprises of a characteristic honeycomb pattern in which the carbon is rolled into seamless cylinder, thereby forming thin cylindrical form of carbon which eventually results into a wide dynamic range of electromagnetic absorptions (Chatterjee et al. 2011). The property of radio frequency (RF) waves by the virtue of which they penetrate deep into the tissue and subsequently release

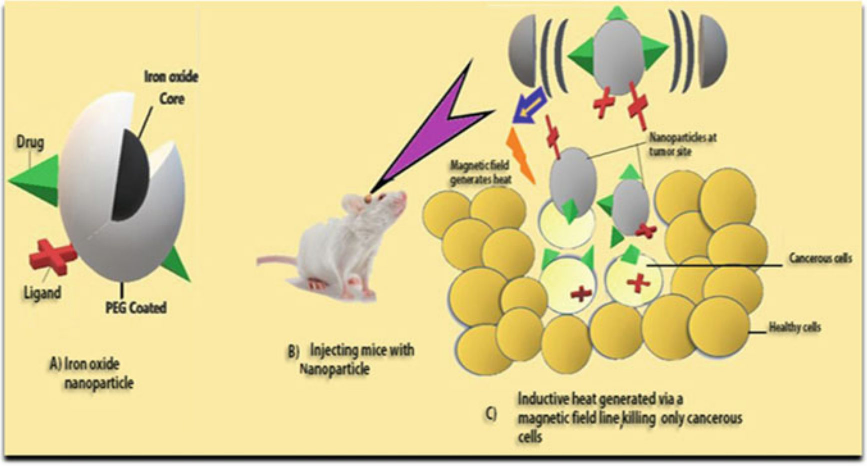

Fig. 19.7 Schematic representation of targeted hyperthermia using nanoparticles. The targeted nanoparticles bind at the cancer site. The external excitation, in the form of either magnetic field or NIR light is applied, they get excited and release energy. Due to targeted accumulation of the nanoparticles at the cancer site, the total energy released at cancer site becomes very high that results in the death of the cancer cells without harming the normal cells

huge amounts of heat has been used in previous works by integrating it with the thermal properties of SWNTs to induce necrosis or apoptosis which kills the diseased cell (Chatterjee et al. 2011). Besides, wrapping of targeting moieties in non-covalent manner or the direct covalent functionalization can be employed to target CNTs, thereby delivering them to specific target (Chatterjee et al. 2011).

Chemo sensitization can also be achieved with the help of hyperthermia. The study to examine the effectiveness and feasibility of the combination of chemotherapy and hyperthermia which was assisted with magnetically guided NPs in order to treat tongue cancer in a rabbit model and the findings revealed the anti-cancer effects showcased by the nanoparticles while they were being exposed to the external alternating magnetic field (Sato et al. 2016). It has been shown and proved that factors like disease type, drug type, drug concentration, temperature gradient at the affected site and the time differential existing between the chemotherapy and delivery of heat, does have some of the effect on the chemosensitization, although prior drug resistance does not seem to be a notable factor in the sensitivity to heat. The highest degree of chemosensitization is obtained when the chemotherapy and heat are simultaneously administered while the effects getting diminished at larger intervals between delivery of two therapies. Although, temperatures above 31 °C are associated with enhanced toxicity and lower benefit: risk ratio in the clinical area, however, it has been found from the literature that many chemotherapeutic agents show increment in enhanced cytotoxicity in the temperature range of 30.5–33 °C. The advantageous destruction of the diseased cells, in chemotherapy coupled with hyperthermia, generally increases with milder temperatures and hence there is a reduction in the chemotherapeutic side effects. However, the problem that persists is about the wide domain of variation in the thermal enhancement of any given agent for different diseases. Different agents may have different ratios of thermal enhancement for the same disease and equal degree of temperature elevation (Kaur et al. 2016). This fact makes it clear that the drug chosen at physiological temperature may not be the correct choice at elevated temperature.

Radiotherapy, similar to chemotherapy, has also been found to become more reliable and effective when used with hyperthermia as an accompaniment. No matter how synergistic this effect might seem to be, the temporal relationship holds its ground of utmost importance because the synchronous treatment which produces hyperthermia effect during the course of irradiation comes out to be the most ideal while the heat prior to the radiation is greatly effective than the inverse (Chatterjee et al. 2011). Clinical evidence prove this very fact as previous works have reported an increment in the response rates by 9–26% after the amalgamation of hyperthermia with the external beam radiotherapy for the diagnosis of multiple cancers (Chatterjee et al. 2011).

19.6 Future

The field of nanotechnology and nanomaterials is developing by leaps and bounds, and therefore it becomes tricky to generalize in the context of toxicity and safety. Even though, the in vitro diagnostic procedures are out of the purview of this potential risk, some major concerns still hover over the in vivo applications of nanoparticles, particularly for those being less than 40 nm in size as they have the potential to penetrate the cell with no answer still being found about their fate in the living body. The wide diversity of materials and huge domain of the variation in their size makes it of utmost importance to investigate their latent effect to increase the efficacy of the process.

Identification and discovery of a notable number of proteins and genes have made things easier in the field of clinical biology, however, the way in which these biological units integrate, assemble, and process remains a mystery. Nanoparticle studies emerge as the savior because they provide thorough insight into the complex realm of cell functions and molecular processes involving sophisticated signaling pathways. Besides, nanoparticles play a significant role in making a constructive understanding about how these processes can be manipulated to obtain better results and how the integral components of the cell mingle together to realize a sophisticated task. Nanoparticles find remarkable applications in the field of mechano-transduction as well because highly efficient analytical devices, comprising of NPs, help in in-depth understanding and analysis of the physical relationships existing between the components of the cell which eventually makes it easy to conceive how cells respond to the stimuli of chemical and mechanical forces.

The detection and monitoring techniques incorporating the NPs have always proved to be a great ally in making a clear understanding of the underlying concept behind the biochemical pathways which are involved in injuries and diseases. Biosensors utilizing the capabilities of NPs have shown tremendous success in the arena of identification of those biological molecules which easily pass the surveillance of conventional assays. These systems employing NPs have shown remarkable selectivity and specificity while reacting to the presence of these previously undetected biological molecules, besides assisting in the amplification of the signal for imaging and detection which eventually have made the diagnostic procedures easier.

It is important to appreciate the fact that with time the nanotechnology methods and processes will get even more matured and then it will be no surprise to witness a sharp decline in the technical barriers while adopting and acquiring various NP-based platforms by the biologists for their ongoing and future ventures. There is no shortage of commercial NPs which are available in the market to be used as highly efficient contrast agents in various imaging and detection modalities like MRI and fluorescence imaging. This makes it crucial to properly analyze, evaluate, and assess the effects of the dynamic properties like the shape, size, surface charge, functional groups, and composition of the NPs. These properties have a significant role to play while determining the harmful and toxic effects of NP-based assays both in vivo and in vitro. Hence, there is a need to standardize the fabrication processes as well as the application protocols in order to keep a check on the toxicity issues related to NPs and further investigation is needed so as to conclude with certainty the extent of potential risk posed by the various NP formulations which in turn are to be used in biological systems and applications.

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Chapter 20
Nanotechnology for Aquaculture

Ahmed A. Tayel, Basant E. Elsaied and Amany M. Diab

Abstract As a part of sustainable culture, aquaculture is objectively a very promising activity comparing to other livestock production industries. Practically, aquaculture encounters serious challenges causing numerous drawbacks at multiple levels such as water infection, pond contamination, biofouling, chronic/acute diseases, and postharvest preservation. Researchers and overseers in the aquaculture industry have continually adopted new technologies to overcome most of these serious challenges; nanotechnology is among the prominent technologies to be applied in many aquaculture pundits. The different practical applications of nanotechnology in aquaculture disciplines are to be presented throughout this chapter. The application of nanotechnology in water and wastewater remediation, e.g., disinfection, sterilization, detoxification, and monitoring, is also discussed. The involvement of nanotechnology in aquatic organisms' performance and health in terms of vaccination, drug delivery, monitoring, antimicrobial application, reproduction control, and functional feeding is also mentioned. Additionally, the role of nanotechnology in harvested fish manufacturing, preservation, packaging, and commercialization is emphasized. The current chapter gives an overview about the current and potential nanotechnology applications in aquaculture and the suggestions to get the maximum benefit from it.

Keywords Nanotechnology · Aquaculture · Seafood · Vaccination · Disinfection · Feeding · Fish preservation

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20.1 Introduction

Nanotechnology is atomic and molecular matter controlling at the nanometer scale of 1–100 nm to study, design, create, synthesize, manipulate, and applicate of functional materials, devices as well as systems for matter exploitation of novel phenomena and properties. Worthy mentioning, the US National Nanotechnology Initiative (NNI) defined nanotechnology as “understanding and control of matter at dimensions of roughly 1–100 nm where unique phenomena enable novel applications”. The numbers of nanoscience applications or authorization of patents for inventions were increased significantly in the world (FAO 2016a).

Nanotechnology has vast potential in electronic, materials science, humans, animal food, and agriculture sectors including aquaculture and its application in biological and biomedical sciences for analysis of biomolecules, development of non-viral vectors for gene therapy, cancer therapy, clinical diagnosis, and therapeutics. The majority of the investment in nanomaterial research is in nano-electronics, nanomedicine as well as nanopharmaceutics research. While in agricultural field, nanotechnologies investment is lesser than others in mentioned sectors and thus few nano-technologies and nano products are available in agriculture, aquaculture industry and animal husbandry. However, there is a huge potential for nanotechnology in this important sector which is required for revolution in socioeconomic status for huge population.

Aquaculture is a major global industry with annual production exceeding 50 million tones as well as estimated value of US$ 80 billion (FAO 2009). Global aquaculture production is growing at 6.6% as an average annual rate since 1995. In 2015, the business reached 76.6 and 29.4 million tons of aquatic animals and aquatic plants, respectively. Aquaculture sector is expected to play a significantly vital role in contributing to food security, economic development, and poverty alleviation (FAO 2016b), and will soon overtake capture fisheries (FAO 2008). Benefits of aquaculture include a production of high-quality food for growing population and jobs. But there are many problems associated with the environmental issues (Martinez-Porchas and Martinez-Cordova 2012a, b). Some of the problems that have negative impacts on aquaculture industry include a destruction of natural ecosystems (Rajitha et al. 2007; DeWalt et al. 2002); water pollution (Paez-Osuna 2001; Avnimelech and Kochba 2009); acidification/salinization of soils (Martínez-córdova et al. 2009; Rodríguez-Valencia et al. 2010); eutrophication and nitrification of ecosystems receiving effluents (Crab et al. 2009a, b; Fenaroli et al. 2014; Martinez-Porchas and Martinez-Cordova 2012a, b); chemical contamination (Justino et al. 2016; Sapkota et al. 2008a, b); biological contamination due to non-native species introduction (Krkošek et al. 2007; Molnar et al. 2008); landscape modification (Bentley 2015; Dumbauld and McCoy 2015); and negative effects on fisheries (Granada et al. 2016; Natale et al. 2013) (Fig. 20.1).

Nanotechnology shows many interdisciplinary activities in both agriculture and aquaculture sectors. Aquaculture industry and the fisheries can be revolutionized by nanotechnology with new tools for rapid disease detection, enhancement of fish

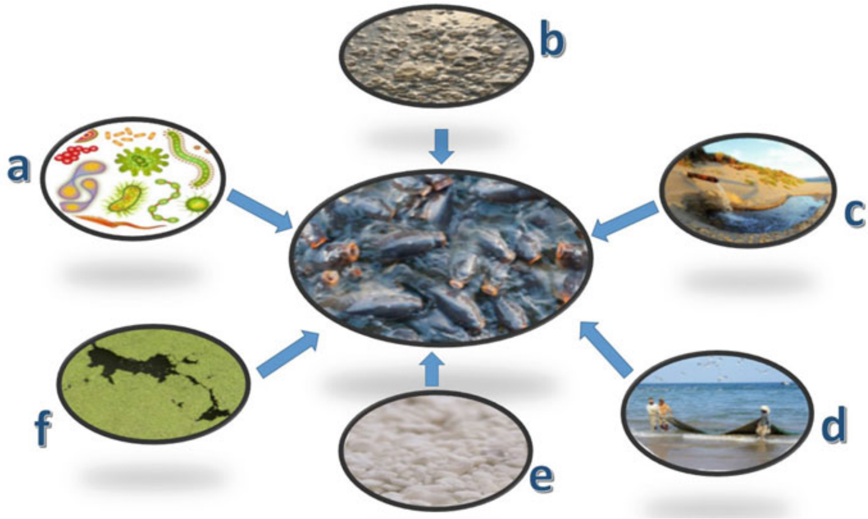

Fig. 20.1 Examples of aquaculture problems concerning environmental issues: **a** biological contamination; **b** water pollution; **c** chemical contamination; **d** fishery problems; **e** soil salinization; and **f** eutrophication. Adopted from Luis et al. (2017)

ability to absorb drugs, vaccines, and nutrients, etc (Rather et al. 2011a, b). Several nanotechnology applications for aquaculture are being developed. The highly integrated fish farming industry may be considered among the best to incorporate

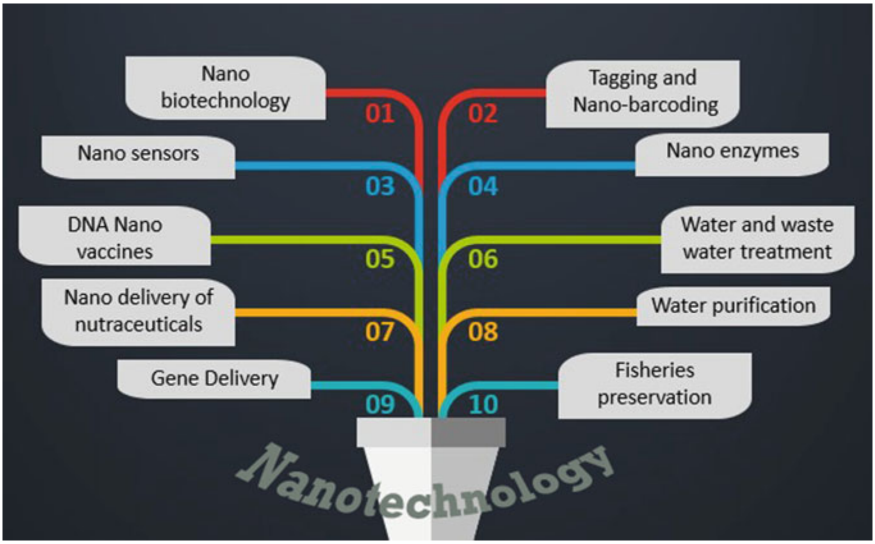

Fig. 20.2 Multidisciplinary activities of nanotechnology in agriculture and aquaculture

and commercialize nanotechnological products (Rather et al. 2011a, b). Moreover, nanotechnology applications in fish processing can also be used to detect fish bacteria in packaging, product safety by increasing the protection during processing (Fig. 20.2).

At present, although the use of nanotechnology in aquaculture needs much of development research, there are many glimpses of the future nanotechnological applications in water treatment in aquaculture, fish health management, animal breeding as well as harvest and postharvest technology.

20.2 Nanotechnology for Clean Water

Water is the life-supporting substance and a precious resource for survival of civilization. Clean water is one of the major global challenges for this century. Aquatic ecosystems and water quality face many old and new challenges. The major factors responsible for water pollution are the human activities; this pollution severely affects fish and may be lethal. So, the need for paying attention to this issue and the necessary corrective measures should be considered (Wang et al. 2015).

Most of fish farm's water is received directly from reservoirs or rivers and is discharged in rivers or reservoirs unfortunately without any previous treatments (Tavares and Santeiro 2013). Fish farms are divided into compartments, such as laboratories for larvae culture, plankton (natural feed) production ponds, fish breeding ponds, fish fattening ponds, and others. Water quality of the mentioned compartments may deteriorate directly because of fertilization and fish feeding management.

Fish farms are maintained by biological interactions as well as complex physical and chemical factors which directly depend on the water quality. Fish farms' wastewater discharged into streams, rivers, or lakes can cause important impacts on the environment (Konsowa 2007). The current water distribution, treatment, and discharge practices are no longer sustainable as these practices heavily depend on conveyance and centralized systems. Nanotechnology not only enable efficient, modular and multifunctional processes, but also provide affordable, high performance to wastewater treatment solutions with minimizing the large infrastructures dependence (Qu et al. 2012). Water treatment technologies based on nanotechnology are used for safe reuse of wastewater, improving sea and saline water desalination, decontamination and disinfection of water, i.e., nano-adsorption and biosorption for contaminant removal, nanophotocatalysis for contaminant chemical degradation, nanosensors for contaminant detection, various membrane technologies including nanofiltration, reverse osmosis, and photocatalysis (Bora and Dutta 2014; Kumar et al. 2014). A basic application of nanotechnology for water resource management has been shown in Fig. 20.3. Some of the aspects are being discussed below.

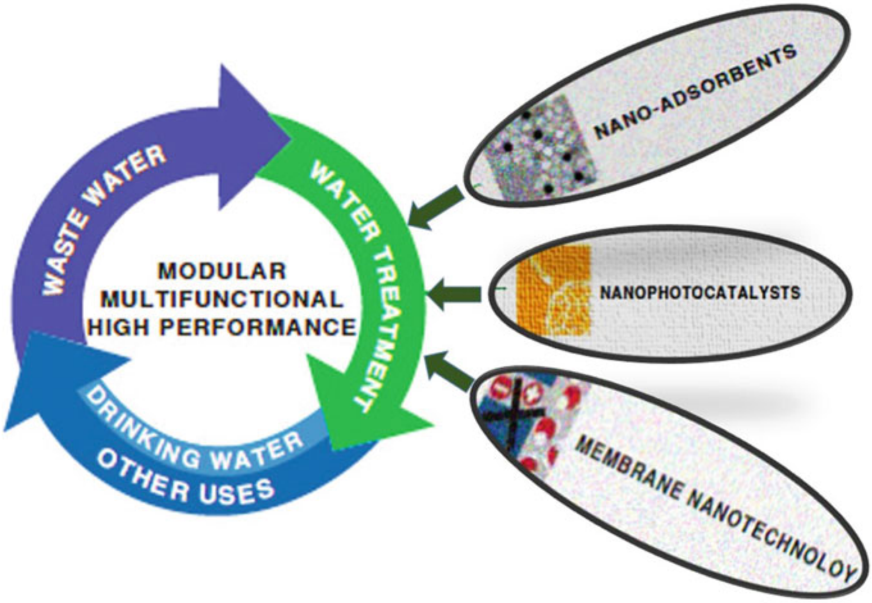

Fig. 20.3 A basic flowchart of nanotechnology for water resource management. Redrawn from Qu et al. (2013)

20.2.1 Disinfection of Water

Water supplies for aquaculture and seed production are often considered as one of the easiest means for infectious disease introduction and spread. A pathogen-free water source is vital for aquaculture success. Surface waters used in aquaculture that come from coastal waters or rivers may contain fish pathogens, so such open water supplies should be treated before use. Parameters such as environmental pollution, soil composition, and food waste can affect the physicochemical properties of pond water in aquaculture (Venkat 2011; 2014a, b), while water quality in open sea or coastal cages is affected by the natural environment (Khosravi-Katuli et al. 2017).

Fish culture facilities should depend on a disease prevention program that includes water quality, quarantine and sanitation of new animals as well as nutritional management. Sanitation practices include disinfection between fish groups, cleanliness during fish growth, and disease transmission prevention by equipment, personnel, or water. Disinfection is a common disease management tool in aquaculture and considered as a part of biosecurity plan by prevention of the target pathogenic agents' entry or exit from an aquaculture establishment or compartment, as well as the pathogenic agents spreading within aquaculture establishments. Disinfection may be used in emergency disease response for supporting the disease control zone maintenance and for eradication of the disease (stamping-out procedures) from affected aquaculture establishments. Disinfection-specific objective will determine the used strategy and how the strategy is applied.

Traditional and time-consuming disinfection process in aquaculture includes surfaces and equipment cleaning and washing for solid waste removal, which may reduce the disinfectants' effectiveness, disinfectant application and chemical residue removal or inactivation to avoid toxicity to aquatic animals as well as corrosion of equipment and environmental impacts. Processes that may be used for chemical residue removal or inactivation may include rinsing of surfaces with water, dilution until the acceptable levels, chemical agents' treatment to inactivate the disinfectant or keeping it for time needed for active compound deactivation or dissipation. Disinfectants may be risks to the users' health and aquatic animals in addition to the environment. Also, there is a need of trained labors, as chemical disinfectants should be used, stored, and disposed of in accordance with manufacturer's regulations and instructions.

Traditional disinfectant methods in aquaculture, such as pH modifiers (alkalis and acids), oxidizing agents, biguanides, quaternary ammonium compounds (QACs), aldehydes, ultraviolet (UV) irradiation, heat treatment, hydrogen peroxide and malachite green, desiccation, or even combined disinfection methods, have several limitations such as high cost, toxicity to aquatic animals, increased pathogen resistance, and negative effects on nontarget organisms (Romero et al. 2012). Still, aquatic establishments including fishponds, tanks, cage nets, pipes, vehicles, containers, buildings, boats, biofilters as well as husbandry equipment need to be disinfected. Moreover, bad water quality may lead to injury to the marine organisms and so results in poor performance (Boyd and Tucker 2012).

Nanotechnology can improve disinfection efficiency, decreasing toxic effects of traditional disinfectants and costs or through augment water supply by unconventional water sources' safe use (Qu et al. 2013). Nanotechnology use in water treatment offers several applications that could be specific to the user, which include nano-adsorbents, nanomembranes, nanometals, nanophotocatalysis, and others. In addition to one useful aspect which is the ability of various properties, integration in multifunctional materials, such as nanomaterials, can be used for simultaneous particle removal and contaminant elimination; hence, greater process efficiency is provided (Gehrke et al. 2015).

Recently, the nano-enabled products' application based on polymers and functionalized composites, aerogels, magnetic engineered and hydrophobic organoclay NPs for treatment and purification of water has been studied (Bhattacharyya et al. 2015; Lofrano et al. 2016). nAg, nAu, nFe, CNTs, nTiO_2, and lanthanum (La) were used for the removal of heavy metal pesticides and ammonia from water as well as wastewater (Ren et al. 2011; et al. 2012; Pradeep 2009; Rather et al. 2011a, b). Quantum dots (QDs) have been proposed for heavy metal detection in aquaculture (Chen et al. 2013), because of their unique optical properties (Vázquez-González and Carrillo-Carrion 2014).

Shrimp- and fish-intensive farming led to growing problems with bacterial pathogens such as *A. salmonicida, Yersinia ruckeri,* and *Flavobacterium columnare* (Pulkkinen et al. 2010). Moreover, aquaculture production has suffered severe losses due to bacterial disease (Huang et al. 2010), but the present traditional sterilization and disinfection methods for aquatic disease control such as various chemical disinfectants and antibiotics have numerous side effects and so many adverse effects (Yang 2003). It is worth mentioning that water disinfection nanotechnologies in fishpond increased water quality, fish and prawn survivals, and so the yields (Huang et al. 2015). In addition, this technology can be applied in both aquariums and commercial fishponds for reduction of water disinfection cost, and believed to provide safe and free fishponds from pollution and disease.

Effective disinfection without toxic disinfection by-product (DBP) formation is a great challenge for water industry. Conventional disinfectants, such as ozone and chlorine disinfectants, can form toxic DBPs (carcinogenic nitrosamines, halogenated disinfection by-product bromate, etc.). While UV disinfection may be an alternative for oxidative disinfection due to minimal DBPs production, but UV disinfection requires high dosage for certain microorganisms (e.g., adenoviruses). So, alternative disinfection development was an urgent need. Nanotechnology has potential role in disinfection and microbial control through many antimicrobial nanomaterials (Li et al. 2008) that have antimicrobial properties, lower tendency to DBPs formation such as nano-Ag, nano-TiO_2, nano-ZnO, CNTs, fullerenes, and nano-Ce_2O_4 (Table 20.1).

Nano-TiO_2 can be taken as an example to understand the antimicrobial mechanisms. These particles could achieve desirable sterilization on *E. coli, Aeromonas hydrophila,* and *Vibrio anguillarum*. In the presence of ultraviolet lights, the sterilizing rate of 0.1 g/L nano-TiO_2 could reach above 98% after 2 h. Moreover, this rate could be still above 96% after 2 h in the sun (Huang et al. 2010). Nano-TiO_2 photocatalytic sterilization efficiency was correlative with nano-TiO_2 concentration and reaction time. Without adequate reaction time or concentration, the sterilization would be ineffective (Huang et al. 2010). Nano-TiO_2 in natural environments has strong sterilization effects but only in sunlight presence as sunlight catalytic effect is like that of ultraviolet without a need of artificial light so this supports this technology application in aquaculture industry. Nano-TiO_2 has organic pollutant

Table 20.1 Nanomaterial antimicrobial mechanisms

Nanomaterials	Antimicrobial mechanisms
Nano-Ag	Release of silver ions, protein damage, suppression of DNA replication, membrane damage
Nano-TiO_2	Production of ROS
Nano-ZnO	Release of zinc ions, production of H_2O_2, membrane damage
Nano-MgO	Membrane damage
Nano-Ce_2O_4	Membrane damage
nC_{60}	ROS-independent oxidation
Fullerol and aminofullerene	Production of ROS
Carbon nanotubes	Membrane damage, oxidative stress
Graphene-based nanomaterials	Membrane damage, oxidative stress

degradation ability in water, disinfection, and sterilization abilities. Under ultraviolet irradiation, it is able to produce free radicals with high oxidation activity such as highly active hydroxyl –OH, peroxyl radical –OOH, superoxide ion –O, and other, which can interact with microorganisms (bacteria and viruses) and bio-macromolecules, such as proteins, lipids, enzymes, and nucleic acid, and other so destroy their cell structures through a series of chain reactions. The end result of these series of reactions is denaturation and lipolysis of bacteria and; accordingly, disinfection and sterilization with efficiency higher than traditional bactericide (Zhao et al. 2000; Yu et al. 2002; Sonawane et al. 2003).

20.2.2 Photocatalysis Using Nanoparticles for Water Purification

Photocatalytic oxidation is an advanced oxidation process for trace contaminant removal as well as microbial pathogens. This process is a useful pretreatment means for enhancing the biodegradability of non-biodegradable and hazardous contaminants. The major barrier for photocatalysis wide application is the slow kinetics due to limited light influencing and photocatalytic activity. Table 20.2 focuses on increasing photocatalytic reaction kinetics and photoactivity range by nano-TiO_2.

In water/wastewater treatment, TiO_2 is the most vastly used semiconductor photocatalyst such as low toxicity, high chemical stability, low cost, and raw material abundance. It generates an electron/hole (e^-/h^+) pair upon UV photon absorption and then later either migrates to the surface to form reactive oxygen species (ROS) or undergoes forming undesired recombination.

The photochemical reaction equation of hole/electron pair produced by photocatalyst (TiO_2) under light is as follows:

$$\text{“}TiO_2 + \text{light energy}(hv) \rightarrow \text{electron}\,(e^-) + \text{positive hole}\,(h^+)\text{”}$$

The hole/electron reacts with the object surface and water in the air, and then reactive free radicals (positive hole) are produced as follows:

$$\begin{aligned}\text{“}h^+ + \text{water molecules}\,(H_2O) &\rightarrow OH + H^+ \cdot \text{electron}\,(e^-)\,\text{and oxygen}\,(O_2)\\ &\rightarrow \text{Reactive Oxygen Species}\left(O_2^-\right)\text{”}\end{aligned}$$

The oxidation–reduction reaction occurs between the hole/electron pairs produced by photocatalyst reaction with organics on the matter surface as well as in the air, which then may be oxidized completely to other innocuous substances and water. Photocatalysis degradation is suggested to involve the (e−/h+) pair generation which is leading to radical formation such as superoxide radical anions,

Table 20.2 TiO_2 photocatalyst optimization

Optimization objects	Optimization mechanisms	Optimization approached	Waste treatment applications
Expanding photoactivity range	• Band gap narrowing	Anion doping	Low-energy cost solar/visible light-activated photocatalytic reactors
	• Impurity energy levels	Metal impurity doping	
	• Electron injection	Narrow band gap semiconductor doping	
		Dye sensitizer doping	
Enhancing kinetics of photocatalytic reaction	• Better electron–hole separation, lower electron–hole recombination	Noble metal doping	High-performance UV-activated photocatalytic reactors
	• Shorter carrier diffusion paths in the tube walls, higher reactant mass transfer rate toward tube surface	Nanotube morphology	
	• Higher reactant sorption, better electron–hole separation, lower electron–hole recombination	Reactive crystallographic facets	
	• More surface reactive sites, higher reactant adsorption, lower electron–hole recombination	Size	

hydroxyl radicals as well as hydroperoxyl radicals. These radicals act as oxidizing species in the processes of photocatalytic oxidation (Gupta and Kulkarni 2011). On the other hand, hydroxyl radicals [OH], reactive oxygen as well as other activated substances can be generated after the hole/electron pair's reaction on surface of the matter in water and air (Zhao et al. 2005). Nano-TiO_2 photoactivity can be improved by optimizing particle shape and size, reducing e^-/h^+ recombination by maximizing reactive facets, noble metal doping, and surface treatment to contaminant adsorption enhancement.

TiO_2 size plays an important role in its sorption, solid-phase transformation, and e^-/h^+ dynamics, where TiO_2 crystalline structures, the most stable for particle size larger than 35 nm, are rutile, while anatase is more efficient in ROS production and is the most stable at particle size smaller than 11 nm (Fujishima et al. 2008; Zhang and Banfield 2000).

The major cause for slow TiO_2 photocatalysis reaction kinetics is the fast e^-/h^+ recombination. Reduction of TiO_2 particle size decreases e^-/h^+ volume recombination as well as improves interfacial charge carrier transfer (Zhang et al. 1998). However, when particle size is reduced to several nanometers, surface recombination dominates, decreasing photocatalytic activity. TiO_2 nanotube organic compound decomposition was recorded to be more efficient than that of TiO_2 nanoparticles (Macak et al. 2007), where the higher photocatalytic activity was related to the shorter carrier diffusion paths in walls of the TiO_2 nanotubes in addition to reactants' faster mass transfer toward the TiO_2 nanotube surface.

In addition to TiO_2, tungsten trioxide (WO_3) and some fullerene derivatives have the potential to be used in water treatment through photocatalysis. WO_3 band gap is narrower than that of TiO_2, and this allows it to be visible light activated, <450 nm (Kominami et al. 2001). Platinum (Pt) can enhance WO_3 reactivity by facilitating O_2 multi-electron reduction and improves e^{-}/h^{+} separation (Kim et al. 2010). Aminofullerenes generate $^1O_2$ under irradiation of the visible light (<550 nm) (Lof et al. 1995) and have been studied for pharmaceutical compound degradation and virus inactivation (Lee et al. 2010). Fullerol and C_{60} encapsulated with poly (*N*-vinylpyrrolidone) under UVA light can produce $^1O_2$ and superoxide (Brune in oxidationt et al. 2009). Aminofullerenes can be immobilized more than fullerol; moreover, aminofullerenes are more effective in disinfection purposes. This is related to their positive charge. TiO_2-produced hydroxyl radicals is higher than $^1O_2$ in oxidation potential, and it has more selective ROS that are less sensitive to nontarget background organic matter quenching. Currently, TiO_2 is much cheaper and readily available than fullerenes.

Photocatalytic water treatment process efficiency strongly depends on the photoreactor configuration and operation parameters. The commonly used two configurations are slurry reactors and immobilized TiO_2 using reactors. A different dispersion/recovery or immobilizations of catalyst techniques are being studied to maximize its efficiency. Recently, the water quality effects and operating parameters include: contaminant type and concentration, TiO_2 loading, temperature, dissolved oxygen, pH, wavelength, and intensity of light (Chong et al. 2010).

Some commercial product, e.g., Purifics Photo-Cat™ system, had treatment capacity up to 2 million gallon/day, with a 678 ft^2 minor footprint. Pilot tests indicated that this system is exceedingly efficient for eliminating organics without waste stream generation and can be operated with low power consumption (Al-Bastaki 2004; Benotti et al. 2009; Westerhoff et al. 2009).

Nano-TiO_2 expedited solar disinfection (SODIS) has been extensively examined and appears to be a possible option for safe drinking water production in developing countries' remote areas. The SODIS system can be either small scale for one person or enlarged to solar compound parabolic collectors of medium size. However, there are many technical challenges for its application on the large scale, including optimization of catalyst for improving quantum yield or visible light utilization; efficient design of photocatalytic reactor as well as catalyst recovery/immobilization techniques; and better reaction selectivity. Along with TiO_2, CeO_2 nanoparticles and carbon nanotubes have been examined in heterogeneous catalytic ozonation processes as catalysts can provide fast and relatively complete organic pollutant degradation. Both radical-mediated reaction pathway and non-radical-mediated reaction pathway have been proposed (Nawrocki and Kasprzyk-Hordern 2010). In both mechanisms, ozone and/or pollutant adsorption on the surface of catalyst plays a critical role.

Nanomaterials' high catalytic activity is related to large specific surface area in addition to an easily accessible surface. Some nanomaterials were also stated to promote ozone decomposition into hydroxyl radicals and facilitate the degradation process by radical-mediated routes (Orge et al. 2011). For industrial-scale applications, the nanomaterial enabled catalytic ozonation mechanism better understanding is a critical need. Moreover, the role of photocatalytic sterilization in aquaculture needs more research.

20.3 Use of Manufactured Nanomaterials in Aquaculture

Water pollution treating nano-adsorption material at present is broadly divided into: TiO_2 class, carbonaceous nanomaterials, iron and iron compounds, and other nanomaterials (McIntyre 2012), In the Lake Biwa, Japan, many kinds of manufactured nanomaterials (MNMs) were used to purify the lake water and the effect was significant (Cao et al. 2015). A similar experiment was carried out in some areas of Shanghai, Suzhou, and good results were achieved. MNMs are used for a month, eliminated the water body odor, and dropped NH_3–N content from 7×10^{-6} to below than 0.5×10^{-6} mg/l, without water change, no oxygen, no side effects, and no secondary pollution (Cao et al. 2015).

Insect Museum of Shanghai used MNMs in a 30 m^2 ponds of ornamental fish with stocking of 40 kg for six months without water change or oxygen addition or sewage suction but with usual feeding fodder, the water NH_3–N content fell from 0.5×10^{-6} below to 0.25×10^{-6} mg/l (Cao et al. 2015).

MNMs were also successfully used by researchers in India for industrial wastewater treatment, good results were achieved, and the investment was covered through power and all vital savings in consumption (Sreeprasad et al. 2013). MNMs were used in the seawater *Cyclina sinensis* nursery, where nanosilver powder, tourmaline nanomicron powders, and other materials were used to improve water quality, purify water, and so get better water environment, resulting in the increased survival rate and improving spat nursery production (Yang et al. 2006). Carbon nanotubes were used to adsorb industrial wastewater containing heavy metals such as zinc, copper, arsenic, chromium in addition to other heavy metals as well as nitro and amino compounds and other greater toxic substances of the dyes. The adsorption process increased with increase of both carbon nanotube dosage and the temperature (Shahryari et al. 2010).

20.3.1 Application in Aquaculture Facilities

In aquaculture field, MNMs application is most widely used in different breeding facilities. According to the physical nature of MNMs applications, they were classified into: nanocoating, nanofibers and nanofilms. In aquaculture, nanocoating has been used as functional, protective, and decorative coatings with other special features such as anti-virus, pest control, anti-fire, and others (Colvin 2003). Moreover nanocoatings' biological function includes two aspects like releasing of the component in coating for biological growth inhibition, so preventing biofouling, and slow release of nutrients that play an important role in organisms' growth (Simchi et al. 2011).

Addition of the nanoscale particle size in surface coatings improves its response to chemical catalysis and photocatalysis and the self-cleaning ability under UV. ZnO nanoscale particles added to paint make nanocoating that has bactericidal, anti-virus activities as well as has a shield UV and infrared absorbing properties (Simchi et al. 2011). Antimicrobial nanomaterial-coated sea cage mesh does not need frequent washing and cannot be fouling. The nutritious nanocoating-coated equipment in the water can breed some organisms on the surface such as unicellular algae and bait; thus increasing the production (Simchi et al. 2011).

Regarding nanofiber, there are studies that proved the strong degradation of toxic substances such as some nerve gases by Pt and TiO_2 nanoparticles; so mixing nanofibers with these groups of similar functions is a good mean for manufacturing high-performance protective suits (Bergshoef and Vancso 1999). In 1999, Professor Mac Diarmid, From the Faculty of Chemistry at Pennsylvania University, who has been awarded the Nobel Prize, proposed a composite nanofiber and reported that "a lot of metal nanoparticles can be very destructive to marine microorganisms." Nickel and copper nanoparticles have been used to make a macromolecule nanofibers acting as a coating material. Subsequently, this coating material that coats the device will produce a small current of waves which prevent marine organisms adhering on the device surfaces; thus, long-term preservation of water-exposed equipment's will not be difficult (Feng et al. 2010).

In aquaculture, filtering media is extremely demanded; the effectiveness of filtering is closely related to the medium fiber fineness. As the filtered material size particle should match both the filtering medium constitutional unit and the passageway, so by applying nanofibers in the medium, the nano-level granules either in the solution or in the gas can be removed (Graham et al. 2002; Tsai et al. 2002). In accordance with a relevant report (Kim 1997), microfiber filters can filtrate aerosol; therefore, these filters are suitable for purifying air. The nanofiber compound and certain selective reagents are used for manufacturing and developing molecular filters that are not only able to separate organic gas and vapor as well as O_2 and CO_2, but also can be useful in biochemical experiments for the toxic reagent removing and so on.

Nanofilm is divided into particle film and dense film. In aquaculture, nanomembrane filtration is using nanomembranes for selective permeability for a different valence ion, water bleaching, natural organic as well as synthetic organic compound removal (such as pesticides), by-products of disinfection removal (THMs and haloacetic acids) in addition to their precursors, for the water biological stability (Savage and Diallo 2005). According to reports, at early 2008 in Zhangjiagang on the anion nanofilm use to experiment, the obtained results suggested that the MNMs polyculture pool facilities of aquatic animals' use improved the quality of water, reduced the disease incidence, and accelerated the growth of animals (Albanese et al. 2012).

20.3.2 Biofouling Control

Nanotechnology may improve aquaculture production and shrimp culture through improving the disease control, feeding formulation, and biofouling control. Biofouling is unwanted bacteria (as biofilm), and invertebrates (mussels and barnacles) and algae (seaweeds and diatoms) could be controlled by coating or paint nanostructuring through metal oxide nanoparticles such as ZnO, CuO, and SiO_2 incorporation. This will be achieved by developing an efficient antifouling surface as well as improving the antifouling control performance (Rajeshkumar et al. 2008; Handy 2012).

The bacterial biofilm allows macrofouler attachment, as in maricultural cages so causing many serious problems such as weight increase, corrosion, surface alteration as well as submerged structure distortion (Champ 2003). Antifoulings are directly applied to get rid of these fouling organisms, but unfortunately on the other nontarget species there are undesired adverse effects, e.g., tributyltin or TBT (Lofrano et al. 2016). nZnO, nCuO, and nSi seem to be potential good antifouling candidates (Rather et al. 2011a, b), because of their high surface–volume ratio producing a more efficient antifouling barrier (i.e., at equal or lower concentrations). Ashraf and Edwin (2016) recorded a significant fouling reduction by using nCuO to treat nets of cage after 90 days from application.

Some commercial products (NanoCheck®) were developed for management of the fishpond using particles of 40-nm size based on lanthanum (La) compounds, which limited the growth of algae through supporting the water phosphate absorption (Mohd Ashraf et al. 2011). Moreover, NPs of La oxides were used on *Escherichia coli*, *Penicillium roqueforti*, *Staphylococcus carnosus,* and *Chlorella vulgaris* as phosphate scavenger resulted in starvation of the microorganisms (Gerber et al. 2012). Vijayan et al. (2014) examined nAg as well as nAu bacterial anti-biofilm activity. The examined nanosubstrates were synthetized from the extracts of *Turbinaria conoides.* The results indicated that nAg only was efficient in biofilm formation controlling, but nAu was not.

20.3.3 Nanodispersants

Oil spill response involves different technologies; one of them used chemical dispersants that contain surface-active agents (surfactant molecules) that agents migrate to the oil/water interface and then reduce interfacial tension between water and oil. With the wave energy abietane, tiny droplets of oil from the oil slick break away. These tiny droplets get dispersed and suspended into the water column, thereby becoming a good food source for the naturally occurring bacteria. The biodegradation process is catalyzed by the dispersants leading to spilled oil removal.

20.3.4 Nanomembranes

Manchester Institute of Technology developed nanowire membranes that have absorbent and superhydrophobic activities for oil selective absorption from an oil–water mixture. This could be achieved by using self-assembly method; this institute has constructed freestanding membranes including inorganic nanowires have the ability of oil absorption up to twenty times their weight. Moreover, MIT's SENSEable City Laboratory has recently produced robot called "Sea swarm" depending on the nanowire mesh. This autonomous oil-absorbing robot uses oil-absorbing nanowire mesh covering a conveyor belt. When the robot moves along the water surface, the conveyor belt as well as the nanomesh rotates, and selective absorption starts for water cleaning. These robots have the ability to run for weeks to clean up several oil gallons per hour using very little energy (as low as about 100 W).

Oil spills generally result in seawater contamination due to water-soluble crude oil fraction dissolution. The contaminated water is highly toxic due to high dissolved hydrocarbon concentration and able to cause ecosystem irreparable damage. The oil-contaminated water photocatalytic decomposition by using TiO_2 particle nanoscale or microscale can control the problem. Professor Feng from Tsinghua University, in collaboration with the other institutions, has produced a new functional nanomaterials (Fig. 20.4) act as an oil–water separation membrane. These nanomaterials can perform efficient separation for a series of oil–water mixture within minutes, and the efficiency of separation was over 99% (Gao et al. 2013).

20.3.5 Desalination

Seawater desalination in the near future will be a major freshwater source because of limited freshwater resources. Reverse osmosis (RO) membranes are high-cost

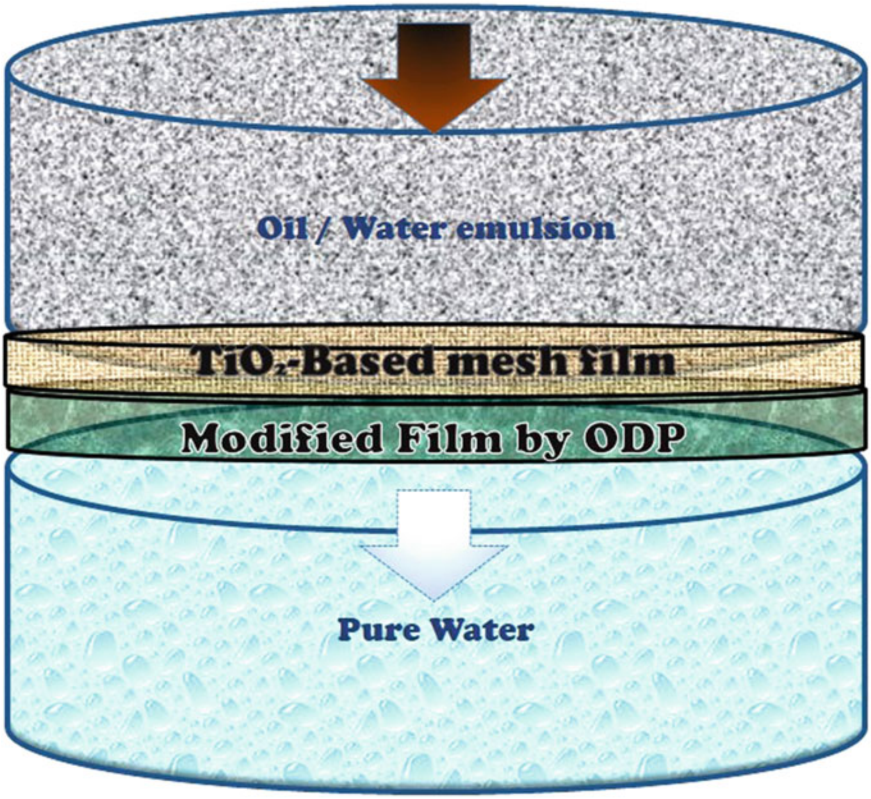

Fig. 20.4 Gravity-driven oil–water separation

conventional desalination technologies due to large amount of energy consumption. Nanotechnology has played a very vital role in creating low-energy alternatives, among which the most promising technologies are: aligned carbon nanotube membranes, protein–polymer biomimetic membranes, and thin-film nanocomposite membranes (Hoek and Ghosh 2009; Nikonenko et al. 2014). These technology desalination efficiencies are up to 1000 times better than that of RO, because it has the high permeability of water due to carbon nanotube membranes present in their structure, and integration of these membranes (some of them) in other processes such as disinfection, defouling, deodorizing, and self-cleaning. In another technology for seawater desalination, zeolite nanomembrane is used (Liu and Chen 2013). Soon, some of these desalination technologies may be present in the market place but there are critical challenges that should be considered as practical desalination effectiveness, scale-up fabrication as well as long-term stability (Ranjan et al. 2016b; Shivendu et al. 2016).

Recently, many devices have been developed with improved efficiency and performance that are self-sustained webs of polyvinylidene fluoride electrospun nanofibers (Essalhi and Khayet 2014); PVA/PVDF hollow fiber composite membrane modified with TiO_2 nanoparticles (Li et al. 2014a, b); novel integrated system coupled with nanofluid-based solar collector (Kabeel and El-Said 2013, 2014); zinc oxide micro-/nanostructures grafted on activated carbon cloth electrodes (Myint et al. 2014); tubular MFI zeolite membranes (Drobek et al. 2012); titanium oxide nanotubes/polyethersulfone blend membrane (Abdallah et al. 2014); graphene-wrapped MnO_2 nanostructures (El-Deen et al. 2014b); thin-film nanocomposite membranes (Subramani et al. 2014); graphene/SnO_2 nanocomposite (El-Deen et al. 2014a); and carbon nanotubes (Goh et al. 2013).

20.3.6 Removal of Heavy Metals

Ligand-based nanocoating can be used for effective heavy metal removal, which is related to high absorption tendency and cost-effectiveness as it can be regenerated by treating with the previously used nanocoating media bifunctional self-assembling ligand in situ. Crystal clear technology is used for water purification in this technology; multiple metal layers are bonded to one substrate (Farmen 2009). Nowadays, nanomaterials have been widely used for heavy metals removal from water/wastewater due to their high reactivity and large surface area.

Metal oxide nanoparticles, such as nanosized ferric oxides, aluminum oxides, manganese oxides, cerium oxides, magnesium oxides, and titanium oxides, have high surface area as well as specific heavy metal adsorption affinity from aqueous systems. To date, development of new technologies for metal oxide nanoparticle synthesis as well as of better possibility for practical use, i.e., composite materials or granular oxides, has become a hot topic to evaluate their heavy metal removal under different experimental conditions or to reveal the metal removal underlying mechanism based on mathematical models or analytical techniques such as XAS, NMR, and ATR-FTIR (Hua et al. 2012; Kumar and Chawla 2014).

Additionally, fulvic acid and humic acid are very common in aquatic environments in addition to have several of functional groups which help them to complex with metal ions as well as interact with nanomaterials. These interactions can alter the nanomaterials' environmental behavior and influence the heavy metal removal and transportation by nanomaterials. Thus, these interactions and their underlying mechanisms need specific investigations.

Tang et al. (2014) have recorded a detailed review on the humic acid and fulvic acid effects on heavy metal removal from aqueous solutions by different nanomaterials, mainly including iron-based nanomaterials, carbon-based nanomaterials, and photocatalytic nanomaterials. Moreover, this review discussed the interaction mechanisms and evaluated the humic acid and fulvic acid potential environmental implications to nanomaterials as well as heavy metals.

Chitosan nanoparticles as adsorbents are being used for the removal of heavy metal. Recent studies have focused on removal of heavy metal by chitosan nanoparticles with clays such as kaolinite, bentonite, and montmorillonite because of the inherent capability of clays to heavy metal removal just like chitosan and chitin. In the recent period, studies on nanochitosan–clay composite for removal of metal ion have been reported (Futalan et al. 2011; Pandey and Mishra 2011). Chitosan–magnetite nanocomposites were also stated for heavy metal removal from aqueous solution (Namdeo and Bajpai 2008; Fan et al. 2017).

20.3.7 Selective Removal of Nitrate and Phosphate

Excessive phosphorus (P) and nitrogen (N) release into runoff from activities of human is eutrophication major cause, which degrades ecosystems and freshwater. Nitrate and phosphate pollutants can be removed by biological treatment, chemical precipitation, membrane processes, ion exchange, electrolytic treatment, and adsorption process for effective removal of these pollutants from water sources (Fig. 20.5).

Ideally, the expected properties of designed zero-valent metal-containing nanoparticles (ZVMNPs) for water treatment include their low toxicity to the biota; high reactivity for the targeted contaminants removal; after injection, high reactive longevity and high mobility in porous media (Yan et al. 2013). Moreover, lowering the enhanced nitrate removal, pH is lowered by adding either buffer system or acidic solutions. Removal of phosphate by iron oxide nanoparticles and

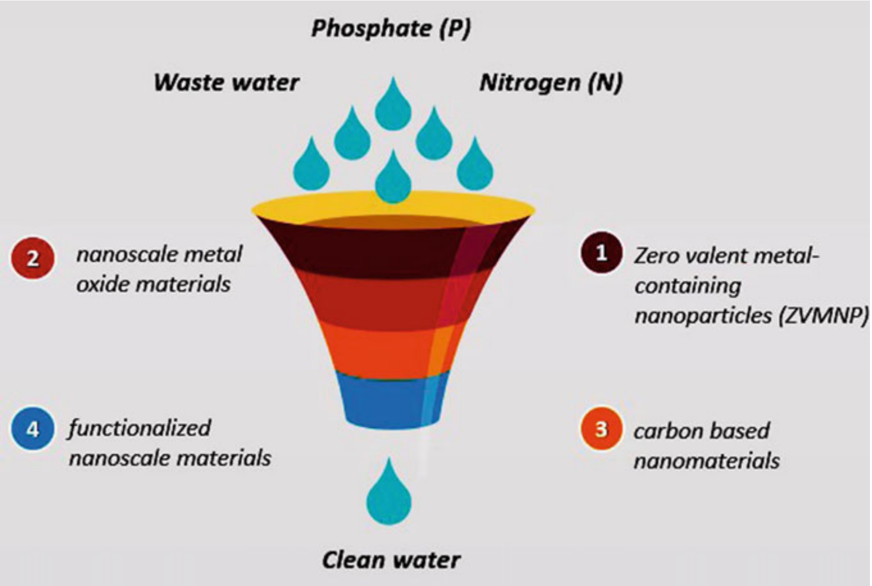

Fig. 20.5 Nanotechnological techniques for removal of nitrate and phosphate ions from wastewater

NZVI is a sorptive process where the sorbed phosphate either still in the nanoparticles or get precipitated with iron species (Prashantha Kumar et al. 2016).

Almeelbi and Bezbaruah (2012) have detected that phosphate is removed up to 100% by using of nanoscale zero-valent iron (nZVI) particles; moreover, nZVI particles had more efficient activity than larger-sized particles (micro-ZVI). Alessio (2015) have reported that nitrate removal efficiency reached up to 98, 87, and 63% in 60 min during the solution treatment from initial concentrations of nitrate nitrogen that were 50, 70, and 95 mg/L, respectively, and verified interaction was found to be a first-order kinetic type.

Among the used adsorbents for water quality standard improvement, hydrated metal oxides, e.g., Fe (III), Zr (IV), and Cu (II) nanocomposite, were extensively explored for removal of phosphate via outer-sphere complexes (Chen et al. 2015). Carbon-based materials like graphite oxide (GO), graphite, graphene, multi-walled carbon nanotube (MWCNT), carbon nanotube (CNT), and functionalized carbon-based materials have made adsorption and catalysis potential applications. Only a few studies for phosphate and nitrate ion removal from aqueous system are reported (Prashantha Kumar et al. 2016).

20.4 Nanotechnology Devices for Aquatic Environment Management

Nanotechnology application in seawater shrimp aquaculture indicated that the nanodevice was able to reduce the water exchange rate and improve both water quality and survival rate of shrimp and so yield (Wen et al. 2003). Among many nanodevices, the best device was nanonet treatment; the results showed fish survival rate increased to 100%, decreasing in both water nitrite and nitrate; moreover, nitrite decreased to as low as 1/4 of the control group. Also, nanotechnologies increased the water pH and improved significantly the water quality (Liu et al. 2008).

In China at present, nano-863 is widely used agricultural high-tech product. This product is produced by addition of nanomaterials of high-temperature sintering and strong light-absorbing properties with a carrier of ceramic material. Nano-863 has been widely used in breeding of livestock, crop cultivation, and aquaculture (Fig. 20.6).

An experiment studied the effects of nano-863 on the water quality results indicating that nano-863 improves water quality and so is more conducive to fish growth while without water changing for 6 months, NH_3–N, NO_3–N, NO_2–N, and CD contents in the test groups were 0.58, 0.89, 0.13, and 8.95, respectively, and all of these results were lower than the control group with conventional changing of water, i.e., 1.58, 2.33, 0.28, and 19.22. While pH was 7.20 in the experimental group, that was higher than the control group (5.60).

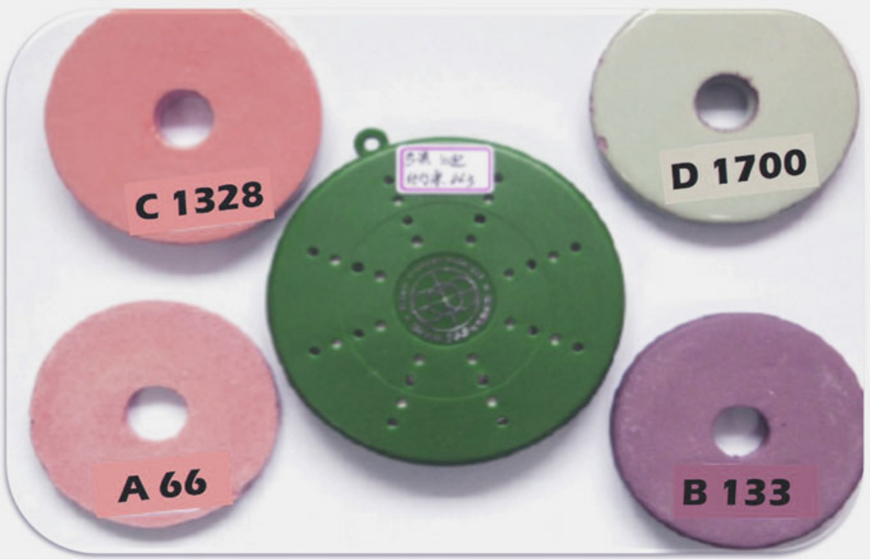

Fig. 20.6 Different types of biological assistant growth apparatus ceramic disks. Qiangdi nano-863 (the biggest green one in the center), Suzhou Zhongchi (a, b, c, and d disks around)

In shrimp farming, nano-863 was used in fishery aquatic breeding farm. A number of million tailed shrimps were tested in each of the control and experimental groups; only 360 thousand survived in the control group, while 730 thousand tailed shrimps survived in the test group; so, the test group survival rate is twice that of the control group. Nano-863 can also enhance water activity and energy, improve shrimp appetite, and so promote growth and development; it also has very strong protection efficacy such as antibacterial as well as disease and algae protection.

Nevada-based Altair Nanotechnologies produce NanoCheck which is water-cleaning product for fishponds and swimming pools. NanoCheck uses 40 nm of a lanthanum-based compound particle that absorbs phosphates from water and so inhibits algae growth (Mongillo 2007). Altair is hoping for NanoCheck use in commercial fish farms worldwide, where heavy metal removal and algae prevention are costly. Altair plans to expand the tests to confirm NanoCheck effect on fish and nanoparticle-laden runoff impacts either on human health or on the environment. Besides, nanoscale delivery of soil-wetting agents and weedicides may be very vital for aquatic weed control in large bodies of water as well as mitigation of stress due to aquatic pollution and climate change. Thai researchers have succeeded in titanium dioxide (TiO_2) nanosized particles used to coat stone or ceramic in fish bowls for water treatment. Ceramics or stones coated with TiO_2 nanoparticles in fish tanks can eliminate bacteria and moss. This technology can be applied in commercial fishponds and aquariums to reduce the water treatment cost.

20.5 Nanotechnology in Fish Health

The aquatic environment is considered as a dynamic medium able to transport pathogens over several kilometers. Furthermore, pathogens are capable of moving between farms, due to the organism's substantial movement and vehicles, which create a highly complex transmission web of disease (Munro and Gregory 2009; Murray 2013). Fish can be infected by various infectious diseases (Khoo 2000; Ramaiah 2006; Brooker et al. 2007; Jacobs et al. 2009; Gomez-Casado et al. 2011; Frans et al. 2011; Oidtmann and Stentiford 2011; Vega-Heredia et al. 2012). Environmental stress is considered a major factor affecting health of fish, such as hypoxia, ammonia poisoning, gas bubble diseases, temperature stress, nitrite poisoning, and pH stress. For infectious disease control, large quantities of veterinary drugs such as antibiotics are employed and, in some cases, resulted in the resistant pests' appearance (Gjedrem 2015; Huang et al. 2015; Lafferty et al. 2015).

There are different administration routes to treat fish, such as the medication dosing into the water (bath treatment), injection, in-feed medication, and topical administration. Bath and topical administration are used for external diseases, while injection and in-feed medication are used for internal infections (Bowker et al. 2016). Various federal as well as state regulatory agencies (such as the US Food and Drug Administration) are regulating drugs used in aquaculture. FDA-approved drugs for use with fish are presented in Tables 20.3 and 20.4 illustrating low regulatory priority (LRP) substances which present little risk to aquatic organisms, the environment, and humans. But these LRP substances can be used with the following conditions: use in the applications listed, appropriate grade when used in animals intended as food, not to exceed prescribed levels.

In addition to antibiotic use in humans, antibiotics are used in treatments of animal for growth enhancement or as prophylactics (Marshall and Levy 2011). However, in aquaculture, antibiotics are frequently used for high productivity ensurance and this has caused the antibiotic-resistant bacteria emergence; moreover, aquaculture ponds are becoming antibiotic resistance gene reservoirs that could be acquired by animal as well as human pathogens (Huang et al. 2015; Letchumanan et al. 2015a, b, c; Tomova et al. 2015; Xiong et al. 2015).

For prevention of diseases, nanotechnology applications include water treatment, pond sterilization, aquatic disease detection and control, nutrients and drug efficient delivery (including hormones and vaccines), and improvement of fish absorption ability of these substances (Bhattacharyya et al. 2015; Huang et al. 2015).

20.5.1 Drug Delivery

Today, probiotics, antibiotics, and pharmaceutical/ nutraceutical application are delivered through injection or feed either as preventive measures or when symptoms are evident. Nanoscale devices may detect as well as treat health problems and

Table 20.3 Drugs approved by the US Food and Drug Administration (FDA) for aquaculture applications

Product	Active ingredient	Manufacturer
Administration route: bath		
Finquel	Tricaine methanesulfonate	Argent Laboratories
Formacide-B	Formalin	B L Mitchell Inc.
Formalin-F™	Formalin	Natchez Animal Supply Company
Halamid® Aqua	Chloramine-T	Western Chemical Inc.
Oxymarine™	Oxytetracycline hydrochloride	Alpharma, Inc
Oxytetracycline HCL Soluble Powder-343	Oxytetracycline hydrochloride	Phoenix Scientific Inc.
Paracide F	Formalin	Argent Laboratories
Parasite-S®	Formalin	Western Chemical Inc.
Pennox 343	Oxytetracycline hydrochloride	Pennfield Oil Co.
Perox-Aid® 35%	Hydrogen peroxide	Western Chemical Inc.
TERRAMYCIN-343 (oxytetracycline HCl) soluble powder	Oxytetracycline hydrochloride	Pfizer Inc.
Tetroxy Aquatic	Oxytetracycline hydrochloride	Cross Vetpharm Group Ltd.
Tricaine-S	Tricaine methanesulfonate	Western Chemical Inc.
Administration route: injection		
Chorulon®	Chorionic gonadotropin	Intervet Inc.
Administration route: in-feed		
AquaFlor®	Florfenicol	Schering-Plough Animal Health Corporation
Romet® TC	Sulfadimethoxine/ ormetoprim	Aquatic Health Resources
Romet 30®	Sulfadimethoxine/ ormetoprim	Aquatic Health Resources
Terramycin® 200 for fish	Oxytetracycline dehydrate	Phibro Animal Health

infections. Nanoscale smart delivery system poses multifunctional characteristics such as pre-programming, time controlling, delivery monitoring of hormones, probiotics, vaccines and chemicals (Donbrow 1991). In medicine, many nanoparticle forms have been used (Table 20.5) such as the nanosized spherical particles which are nanospheres (De Jong and Borm 2008). Nanospheres have high surface area and small size which permit the dispersion of a specific drug on the surface of

Table 20.4 Low regulatory priority (LRP) substances used in aquaculture

Substances	Applications
Acetic acid	Parasiticide
Calcium chloride	Egg hardening and maintenance of osmotic balance in fish
Calcium oxide	Protozoacide
Carbon dioxide	Anesthetic
Garlic	Infestation control of helminths and sea lice
Ice	Metabolism reducer
Magnesium sulfate	Infestation control of trematodes and crustaceans
Onion	Infestation control of crustaceans and sea lice
Papain	Aid in removal of the gelatinous matrix from eggs
Potassium chloride	Osmoregulator and antistress agent
Povidone-iodine	Egg disinfectant
Sodium bicarbonate	Aid in fish anesthesia
Sodium chloride (salt)	Parasiticide, antistress agent, and osmoregulator
Sodium sulfide	Improved hatchability
Thiamine hydrochloride	Prevention of thiamine deficiency
Urea and tannic acid	Reduced adhesiveness

Adapted from Bowker et al. (2016)

Table 20.5 Different forms of nanoparticles used in biomedical applications

Type of nanoparticles	Structure	Application in medicine
Nanospheres	Spherical shaped	Drug delivery, tissue regeneration
Nanocapsules	Shell and core combination	Controlled drug delivery
Carbon nanotubes	Cylindrical tubes	Drug delivery, anticancer
Liposomes	Lipid bilayer globules	Drug delivery for hydrophobic and hydrophilic drugs
Dendrimers	Highly branched ends and central core	Delivery system, tissue engineering, antimicrobials
Polymeric nanoparticles	Polymers such as chitosan and PLGA	Delivery system, tissue regeneration

nanosphere and so facilitate drug delivery. Tissue regeneration is another field where nanospheres can be used (Ramalingam et al. 2013). Nanocapsule is another nanoparticle form, which consists of an inner core and an outer nanoscale shell. The core may be water or oil that contains a specific drug, while the outer shell protects that specific drug from hydrolysis and degradation (Torchilin 2006). Liposomes as an example are lipid bilayer nanosized spheres. Liposomes are ideal for both hydrophilic and lipophilic medications' drug delivery due to their structure that is like the cell membrane of eukaryotes (Lasic 1998; Cavalieri et al. 2014). Carbon nanotubes (single- or multi-walled) are nanoparticle forms commonly used in various medical applications including anti-tumor drugs as carbon nanotubes are characterized by high cell membrane penetration ability and very large surface area. Carbon nanotubes are ideal for drug delivery by acting as micro-needles (Reilly 2007). However, carbon nanotubes have high risk of inducing thrombi in the blood vessels (Gaffney et al. 2015). Dendrimer form is the fourth particle form. Dendrimers are nanoscale three-dimensional structures composed of tree branch-like units originated from a central core. These have low molecular weight with a highly branched multifunctional surface that facilitates dendrimers' use as a delivery system for vaccines, genes, and drugs as well as tissue regeneration scaffold and as antimicrobial agents (Aulenta et al. 2003; Gillies and Frechet 2005; Wu et al. 2015).

In fish medicine, the applied nanoparticle types have been limited to nanospheres or polymeric nanoparticles; other nanoparticle application forms have not been investigated yet.

20.5.1.1 Chitosan Nanoparticles for Drug Delivery

Chitosan nanoparticles are excellent drug delivery vehicles that have characteristic proprieties such as non-toxic, biocompatible, and biodegradable polymer as well as easily excreted from the kidney (De Jong and Borm 2008). Moreover, chitosan nanoparticles can be adapted for sustainable and slow drug release due to mucoadhesive property means (Dutkiewicz and Kucharska 1992). For example, in a study on rainbow trout (*Oncorhynchus mykiss*) vitamin C conjugation with chitosan nanoparticles resulted in vitamin release for 48 h after oral administration, and with led to immune system stimulation due to the potent synergism between vitamin C and chitosan (Alishahi et al. 2011). In another investigation, carried on *Cyprinus carpio*, chitosan nanoparticles were examined as a hormone delivery system. Luteinizing hormone-releasing hormone (LHRH) was bound to both chitosan nanoparticles alone in one group, and in another group LHRH conjugated with chitosan–gold nanoparticles. Both groups' results showed blood hormone levels increase with hormones sustaining release groups, in comparison with the group that injected with hormone alone. Moreover, the rates of egg fertilization were elevated after one injection dose of hormone–chitosan gold nanoparticles and hormone–chitosan nanoparticle conjugate with 83 and 87%, respectively, comparing to LHRH alone multiple injections that gave 74% fertilization rate (Rather et al. 2013).

20.5.1.2 PLGA Nanoparticles for Drug Delivery

PLGA is a copolymer composed of polylactic acid in addition to poly(glycolic) acid. PLGA is biocompatible, non-toxic, biodegradable, and FDA-approved. Hence, many researchers investigated PLGA feasibility as a drug carrier (Lü et al. 2009; Makadia and Siegel 2011). In a study on embryos of zebra fish, the

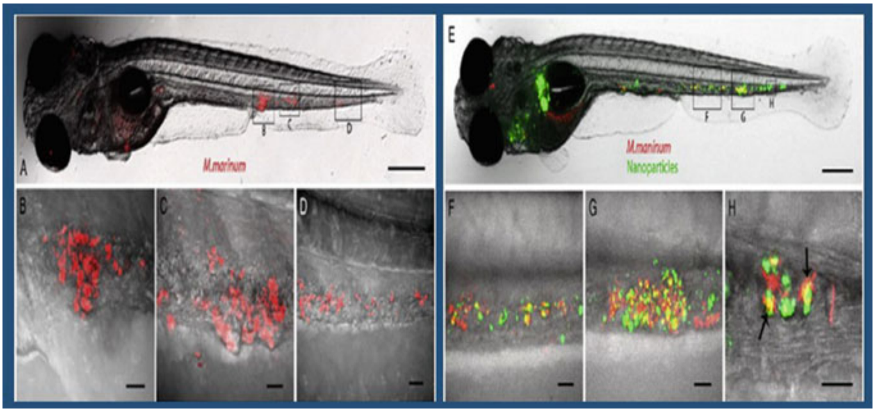

Fig. 20.7 **a**–**d** Lateral view showing formation of *Mycobacterium marinum* granulomas in zebra fish embryos. After injection of nanoparticles in the posterior caudal vein, panels, **e**–**h** show rifampicin-loaded PLGA nanoparticles targeting the granulomas. Adapted from Fenaroli et al. (2014)

anti-mycobacterial agent (rifampicin) was loaded on PLGA nanoparticles and then applied because zebra fish embryos transparency had a vital role in measuring the impact of treatment on *Mycobacterium marinum*-infection using noninvasive imaging (Fig. 20.7). The rifampicin–PLGA nanoparticles achieved increasing of therapeutic effect as well as higher embryo survival against M. marinum compared to rifampicin alone (Fenaroli et al. 2014).

20.5.2 Nanosensors

In aquaculture industry, various diseases caused huge losses annually; therefore, diseases' efficient detection and control are very important for both maximizing productivity and final product satisfactory quality ensurance (Ninawe et al. 2016). Nano-biosensor use offers an innovative means to solve problems. These devices may be depending on different nanomaterials, for example carbon nanotubes could possibly facilitate the detection of low pathogens concentrations including viruses, bacteria, parasites and pollutants (Chen et al. 2016).

Rapid pathogen detection in aquatic organisms may be very effective way to disease control, but the available detection methods are costly, time consuming, and could have detection and separation difficulties for some pathogen (Guo et al. 2016). A study designed an immunomagnetic NP-based microfluidic system for *Staphylococcus aureus* detection producing a microfluidic chip with indium tin oxide. The obtained results evidenced that the detection system sensitivity and specificity were the same results of the colony counting method, with a whole shorter time of detection without colony cultivation.

Sensitive and rapid disease diagnosis adopted for nanoparticles are called nanodiagnostics (Jain 2003). Gold nanoparticles are widely used in diagnostics and considered one of the most used particles, which are suitable for use in different methods (Baptista et al. 2008; Saleh et al. 2015). The first gold nanoparticle report for fish pathogen detection was with *Aeromonas salmonicida* antibody-gold nanoparticles conjugated for furunculosis-specific immunodiagnosis in fish tissues (Saleh et al. 2011). Kuan et al. (2013) prepared an electrochemical DNA biosensor for *Aphanomyces invadans* detection in fish with a DNA reporter probe and based on conjugation of Au-NPs and so fungi which are at a lower level than PCR could be detected.

Jaroenram et al. (2012) combined colorimetric assay of Au-NPs with loop-mediated isothermal amplification (LAMP) for yellow head virus visual detection in shrimp. This was high sensitive, rapid, and specific method. A similar combination of LAMP with DNA-functionalized Au-NPs was developed for white spot syndrome virus (WSSV) detection in shrimp (Seetang-Nun et al. 2013). This method was sensitive, specific, and suitable for field applications. In another study, Toubanaki et al. (2015) designed a method for detection of nervous necrosis virus (NNV) by using gold nanoparticle-based biosensor for viral nucleic acid detection after RT-PCR amplification, but this was quite cost-effective, as this method did not require antibody conjugation.

Yang et al. (2012) recorded an immunomagnetic reduction assay in grouper fish for nervous necrosis virus (NNV) using magnetic nanoparticles covered with rabbit anti-NNV antibody. Application of an external magnetic field, for immunodiagnosis was based on magnetic nanoparticle motility; if the viral antigen bound to antibody coated-nanoparticles and form clusters, that will decrease their motility. The virus titer could be detected using a magnetic immunoassay analyzer. Spring viremia of carp virus (SVCV) detection by a colorimetric assay was developed using unmodified Au-NPs. At first addition of the probe, that was complementary for SVCV and then followed by gold nanoparticles. If target RNA of the virus was present, it hybridized to the probe, so the probe is prevented from stabilizing the gold nanoparticles. The gold nanoparticles could aggregate resulting in the solution change from red to blue. If there was not viral nucleic acid, the probe could be freely adsorbed onto the gold nanoparticle surface; this could prevent nanoparticles aggregation and keep the red color of solution (Figs. 20.8 and 20.9) (Saleh et al. 2011). This method was highly specific and rapid, and there was not a need for prior viral nucleic acid amplification. The same principle was used for developing a specific, rapid as well as sensitive assay for the DNA virus detection, cyprinid herpesvirus 3 (CyHV-3) (Saleh and El-Matbouli 2015).

20.5.3 Nanovaccines

In many infectious fish diseases, main gateway is ecosystem. The natural biological cycle includes one or more hosts' stable association to provide a medium for the

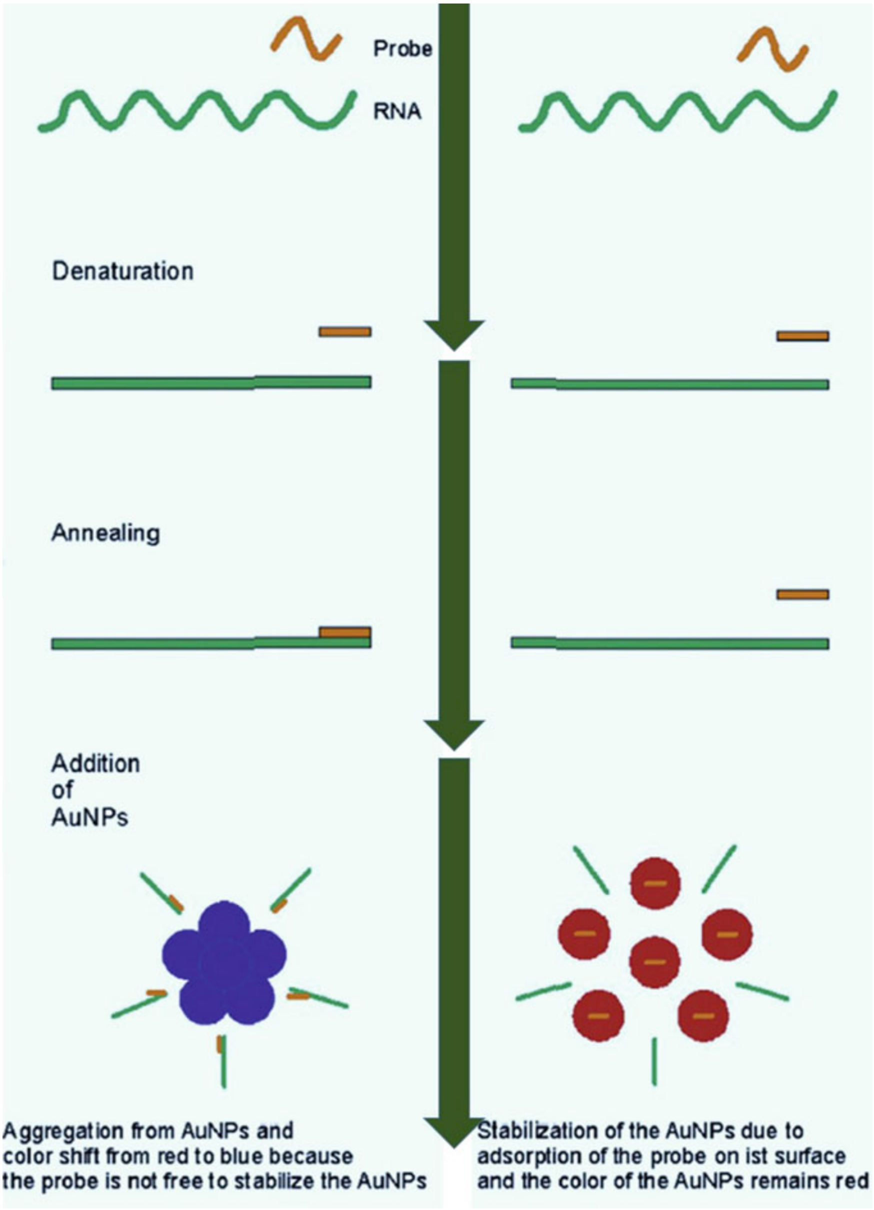

Fig. 20.8 Principle of direct detection of SVCV RNA using unmodified gold nanoparticles. Redrawn after Saleh et al. (2012)

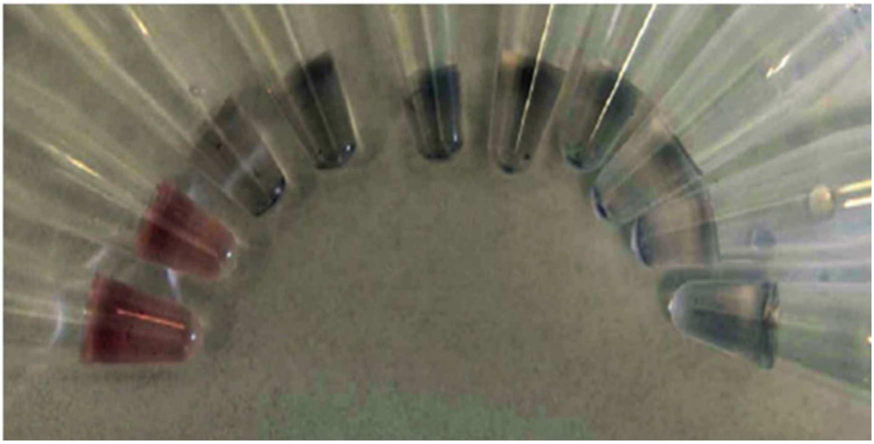

Fig. 20.9 Results of a gold nanoparticle-based assay for detection of SVCV: In a positive test, the color of the solution changes from red to blue. Adapted from Saleh et al. (2012)

pathogen progressive transmission and efficient replication for causing the infection. As infection proceeds, minor variations encounter in the pathogen natural environment, such as host genetics individual variations as well as the immunological response to infection (Alexander and Mewhinney 2008).

The nanotechnological formulation development for aquaculture application has been a major focus of research. An important characteristic of these systems is multiple application suitability, such as the administration of antibiotics, vaccines, nutraceuticals, and other pharmaceuticals (Rather et al. 2011b). Advantages typically include: enhancing the active agents' bioavailability through low absorption, sustained release of the active agent, decrease in application frequency, and high molecular level of dispersion, because of nanoscale size, that can be used in the disease treatment (Can et al. 2011; Bhattacharyya et al. 2015).

Conventionally, the active substance application is achieved either by injections or in the fish food, which can be associated with side effects because of excessive use and substantial losses during the process (Sheridan et al. 2013). The biodegradable nanoformulation production with essential oils can play a vital role in solving the disease control efficiency problems, as well as the contamination problems. The contamination can be decreased by reducing the used traditional chemical in disease control because nanoparticles can act as controlled released systems and thus sustain the biological active compounds amount to treat diseases. Many studies have recorded the synergism between using of essential oils encapsulated in biodegradable nanoparticles (Chifiriuc et al. 2017; Pavela et al. 2017; Sotelo-Boyas et al. 2017a, b).

Several of these studies can play a role in solving aquaculture real problems, where they evaluate the antifungal and bactericidal efficacy and so could be used in fish disease treatment. Recently, Rai et al. (2017) discussed the prospects and emerging trends of the synergism between antimicrobial potentials of essential oils and nanoparticles. Researchers described that the essential oil encapsulation in nanoparticles is a promising strategy where these systems can facilitate these compounds' application as antimicrobial agents. In addition, researchers cited that the active compounds sustained, and controlled release can improve the efficacy and bioavailability against multi-resistant pathogens. Moreover, nanodrugs as well as vaccines might be costless and more effective to prevent/ treat diseases than current technologies (Chen and Yada 2011).

Naturally, vaccination has an important role in fish farming. Nanoparticles use for fish vaccination became a vital criterion, particularly for the farmed fish. Nanoparticles have multifaceted advantages in the administration of drug such as vaccine delivery and improving the farmed fish protection against pathogens that caused diseases. However, the benefits accompanied with nanoparticle distribution may be associated with health and environment risks (Walker 2004). Naturally, polymeric nanoparticles have many advantages in vaccine delivery, such as sustained vaccine delivery, drug solubility for intravascular delivery, and vaccine antigen solubility improving against enzymatic degradation. In aquaculture, the nanoparticles used for vaccine delivery are an interesting possibility but still the precautionary principle needs to be the ideal of the best scientific practice for fish vaccination (Nielsen et al. 2011).

In general, salmon is vulnerable to diseases. Pathogens of fish transmit well in water as well as high stocking densities so the shorter the distances between farms the higher transmission occurs. An excessive antibiotic use may prevent bacterial diseases but again was not environmentally sustainable. The motivation trail for nanoparticle utilization in salmon vaccines relates to that oil-adjuvant vaccines have not been effective against some of intracellular pathogens (importantly viruses) as well as it is difficult to use a strong alternative adjuvant system. Moreover, oil-adjuvant vaccines have unwanted side effects in salmon such as autoimmunity, internal organ adhesion in the abdomen and, less frequently, the deformations of skeleton. Producers of vaccine are continuously trying application of oil adjuvant but with lesser side effects.

Recently, fish vaccine can be developed with poly(lactic-co-glycolic) acid (PLGA) which is a synthetic organic polymer. These particles maintain antigens from premature degradation, i.e., before producing an effective immune response. The PLGA particle degrades in vivo and so releases the antigens over time. The degradation rate of the particles can be prepared by changing copolymer composition as well as particle size, properties that the vaccine efficiency can be sensitive. Au-NPs also play a vital role in fish vaccine release.

Through chitosan nano, vaccine can be delivered. Chitosan nano is able to wrap around vaccines which act as a carrier and are used in nano-encapsulation in the fish physiology for treatment delivery. The bacterium *Listonella anguillarum* nano-encapsulated vaccines can be introduced in Asian Carp (Myhr and Myskja 2011; Rajeshkumar et al. 2009).

Nanocapsules containing nanoparticles can be used in mass vaccination of fish. These will be resistant to degradation and digestion. Nanocapsules contain short

DNA strand that are absorbed into the cells of fish when administrated to water containing fishes. For breaking the capsules, the ultrasound mechanism is used and then the DNA is released, thus improving an immune response to fish by the vaccination. Similarly, these vaccines' oral administration and the active agent site-specific release for vaccination will reduce disease management effort, the cost, drug, vaccine application delivery, etc., at the same feeding cost leading to sustainable aquaculture.

Polyanhydride NPs were used for vaccine antigen encapsulation, and release determines shrimp immunization with feed or via immersion (Ross et al. 2014). Moreover, for drug administration silica-based NPs can be suitable (i.e., pharmaceuticals or other therapeutics) due to the porous structure as well as high dose incorporation ability (Strømme et al. 2009).

Briefly, nanoparticles are applied as oral drug carriers for many reasons, like drug bioavailability improvement with poor absorption characteristics (Florence et al. 1995), residence time prolongation and drug digestive stabilization in the intestine, efficient absorption due to high dispersion at the molecular level, vaccine antigen delivery to gut-associated lymphoid tissue (Jani et al. 1990), and drug release control (Eldridge et al. 1990).

20.5.4 Antibacterial Activity of Metal-Based Nanoparticles

The most investigated nano-antibacterial agent is silver nanoparticle. They have multiple acting mechanisms against bacteria, and so they can evade the resistance of bacteria (Knetsch and Koole 2011), in contrast to antibiotics which have one acting mechanism only (Hindi et al. 2009; Antony et al. 2013). The silver ion (Ag+) release is one mechanism [287]. Ag+ binds to cell membrane proteins of bacteria causing membrane disruption, so leading to the bacterial cell's death (Lara et al. 2010). Intracellularly, Ag+ binds to nucleic acids and cytochrome, damaging them as well as inhibiting cell division (Huang et al. 2011).

Prakash et al. (2013) illustrated that silver nanoparticles possess high antibacterial efficacy against bacterial isolates that have multi-drug resistant. Silver nanoparticles' bactericidal effect has also been demonstrated against methicillin resistant *Staphylococcus aureus* (Ayala-Núñez et al. 2009). Silver nanoparticles synthesized using a reducing agent which was citrus limon juice demonstrated antibacterial as well as anti-cyanobacterial activity against *Edwardsiella tarda*, *S. aureus*, Anabaena and Oscillatoria species, respectively (Swain et al. 2014).

Umashankari et al. (2012) used mangrove *Rhizophora mucronata* leaf bud extract for AgNPs biological synthesis and then demonstrated antimicrobial effects against *Proteus* species, *Pseudomonas fluorescens,* and *Flavobacterium* species. These "green" synthesized silver nanoparticles' efficacy was the same as that of commercial antibiotics. In a study on juvenile shrimp *Fenneropenaeus indicus* infected by *Vibrio harveyi*, silver nanoparticle long-term treatment decreased mortalities by 71% at AgNPs high doses (Vaseeharan et al. 2010).

There is great interest to investigate gold nanoparticle antimicrobial effects, and this is related to that gold nanoparticles have low toxic effect to eukaryotic cells (Li et al. 2014a, b). Gold nanoparticles can interact with biological proteins as well as nonproteins, such as lipopolysaccharides (LPS), and have biological functions (Sumbayev et al. 2013). Au-NPs supporting zeolite have bactericidal effects against *Salmonella typhi* and *E. coli* (Lima et al. 2013). Functionalized Au-NPs inhibited resistant bacterial isolate growth (Li et al. 2014a, b). "Green" synthesized gold nanoparticles possess antibacterial activity against bacteria isolated from fish (Velmurugan et al. 2014).

Gold nanoparticles have three pathways to achieve their antibacterial effects. First way is through oxidative phosphorylation process interference with changing bacterial cell membrane, which leads to decrease in F-Type ATP synthase activity and a net decrease in both ATP synthesis and metabolism. The second path is via interference with tRNA binding to the two ribosome subunits. The third pathway is through enhancing chemotaxis (Cui et al. 2012).

Zinc oxide nanoparticles have antibacterial as well as antifungal effects (Gunalan et al. 2012; Swain et al. 2014). The antibacterial activity is related to damage the particles to the cell membrane of the bacteria and so makes the contents of the cytoplasm leak from the cell (Liu et al. 2009). In the fish medicine field, ZnO-NPs can inhibit Aeromonas hydrophila, *Vibrio* species, *Edwardsiella tarda, S. aureus, Flavobacterium branchiophilum, Pseudomonas aeruginosa, Citrobacter* spp., and *Bacillus cereus* growth (Swain et al. 2014). Ramamoorthy et al. (2013) studied the ZnO nanoparticles' antibacterial effects against *Vibrio harveyi,* and the results indicated a higher bactericidal effect of ZnO-NPs in comparison with bulk ZnO.

TiO_2-NPs had a bactericidal effect, when doped with magnetic Fe_3O_4-NPs against *Edwardsiella tarda, Streptococcus iniae,* and *Photobacterium damselae*, after light activation. Moreover, these particles can be applied for water disinfection, as pathogens of fish bind with the nanoparticles, and then be easily extracted from the water using a magnet (Cheng et al. 2009, 2011). However, Jovanovic et al. (2011, 2015) concluded that TiO_2-NPs could affect immune system of fish though inhibition of fish neutrophils antibacterial activity, and accordingly making fish liable to the infection and hence fish mortality increased especially in outbreaks of the diseases.

20.5.5 Antifungal Activity of Metal-Based Nanoparticles

Silver nanoparticles as an antifungal agent exhibited high inhibitory effects similar to the Amphotericin B (commercial antifungal) against Candida species (Sanjenbam et al. 2014; Mallmann et al. 2015). Silver nanoparticles' antifungal activity against dermatophytes was recorded (Kim et al. 2008). Gold nanoparticles' fungicidal activity was reported against Candida species. Au-NPs efficacy was related to their size, as the smaller the size of gold nanoparticles the higher their antifungal activity (Wani and Ahmad 2013; Ahmad et al. 2013).

In another interesting study, *Aeromonas hydrophila* was used for ZnO nanoparticle biological synthesis, and these nanoparticles had antibacterial activity against *A. hydrophila* (the same bacterium), *P. aeruginosa*, *Enterococcus faecalis*, *E. coli*, *Candida albicans,* and *Aspergillus flavus* as shown in Fig. 20.10.

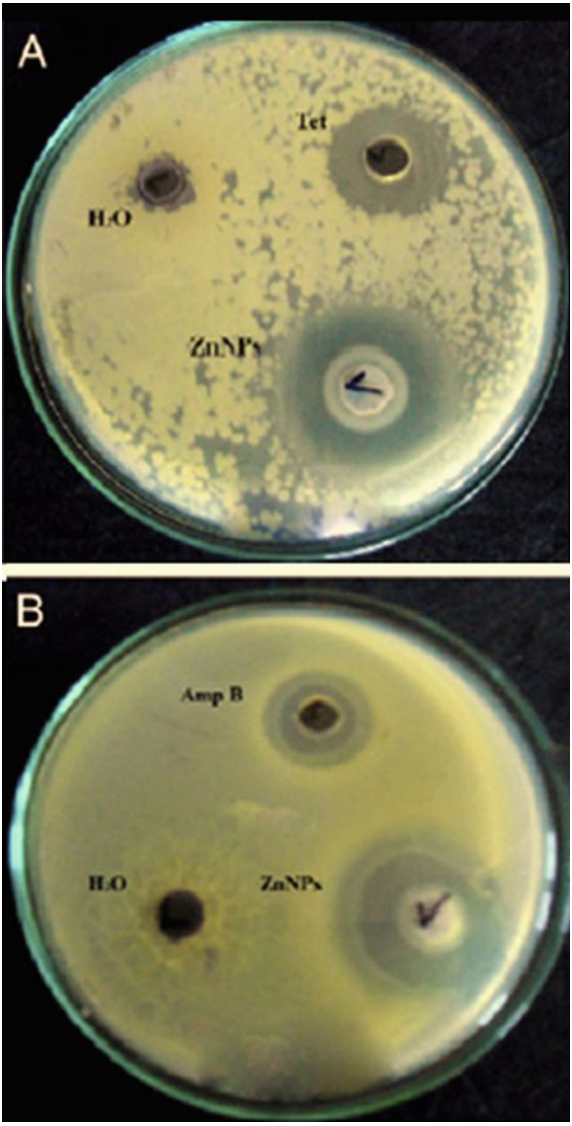

Fig. 20.10 Mueller-Hinton agar plates showing the antifungal effects of ZnO-NPs, and zones of inhibition against both **a** *Pseudomonas aeruginosa* and **b** *Aspergillus flavus*. Adapted from Jayaseelan et al. (2012)

20.5.6 Antiviral Activity of Metal-Based Nanoparticles

Silver nanoparticles also possess antiviral properties such as HIV-1 virus proteins binding activity in vitro (Elechiguerra et al. 2005), active against influenza A virus (both silver nanoparticle–chitosan composite and silver nanoparticles) (Mehrbod et al. 2009; Mori et al. 2013). In fish medicine, little work was published specifically on silver nanoparticles' antiviral and antifungal effects.

20.5.7 Gene Delivery

The new carrier system development for gene delivery acts as an enabling technology for many genetic disorders' treatment. However, a safe and efficient delivery vehicle formulation is considered a critical barrier for gene therapy success. Non-viral systems for delivery were proposed as promising alternatives to viral vectors, due to their stability, safety, and facility to be made in large amounts (Tomlinson and Rolland 1996). Some attitudes employ nanocomposites complexed with DNA containing peptide, protein, lipid, or polymeric carriers. Promising outcomes were achieved from the nanosphere complex formation between chitosan and DNA (Roy et al. 1997).

Ramya et al. (2014) showed the efficient protection of a DNA construct containing nodavirus gene which was extra small virus antisense (XSVAS) encapsulated with chitosan NPs increasing the survivability of *M. rosenbergii*. Nanomedicine in fish is in its infancy, and several gaps about the adverse effects to both target and nontarget species need to be addressed.

20.5.8 Fish Reproduction Control

In commercial aquatic animal artificial reproduction, incomplete vitellogenesis in females is considered one of the most vital and common problems, which is leading to final oocyte maturation as well as ovulation failure. So, there is a necessary need to develop methods for adequately controlling the reproductive process and so overcome this problem. Chitosan NPs can be used in a controlled way to carry and release endogenous hormone (Pulavendran et al. 2011). Rather et al. (2013) studied salmon hormone–chitosan–nAu as a trial to overcome the problem of the reproductive hormones' short life in blood, thus avoiding the multiple injection uses to enhance reproductive efficacy. The achieved results were that in treated organisms the reproductive hormones were present for a longer period in blood and both of the eggs' relative number and fertilization rate were significantly increased. Moreover, chitosan nanoconjugated salmon luteinizing hormone-releasing hormone

(CsLHRH) increased the level of expression to SOX9 transcripts in gonads as well as the levels of steroid hormonal in blood of *Clarias batrachus* female and male, moreover being helpful for proper development of gonad (Bhat et al. 2016).

20.6 Nanotechnology in Fish Feeding

Fish may suffer from nutritional deficiencies due to the improper balance, lack, or excess of food components. In aquaculture, the feed production is considered one of the most important applications of nanotechnology where NPs' use has proved to be effective for micronutrient delivery, growth promotion, and encapsulation of feed.

20.6.1 Micronutrient Delivery

In aquaculture research, an emerging area is nutraceutical use for fish health management, stress mitigation, and value addition in fish as well as shellfish. Despite nutraceutical low requirement, higher application cost is involved. Thus, wastage should be minimized for economic viability and efficient utilization of nutraceutical. Nanodelivery system development for these molecule kinds may address their application problems in aquaculture practices at the commercial level. There is a great opportunity for nanoparticle use to deliver nutraceuticals in feed of fish and nutrigenomics studies. Moreover, many feed nanoformulations help to maintain better consistency as well as feed taste.

Chitosan [poly(1,4-β-D-glucopyranosamine)] is a polysaccharide having antimicrobial potential with low toxicity and low immunogenicity that is being widely used for human and animal feed production (Rather et al. 2013; Luo and Wang 2013; Ferosekhan et al. 2014). Chitosan NPs novel applications for the unstable and/or hydrosoluble micronutrient delivery are in early development stages. Alishahi et al. (2014) showed that chitosan NPs use significantly increased vitamin C delivery as well as shelf life in rainbow trout after feeding for 20 days. Jiménez-Fernández et al. (2014) conducted a similar study for chitosan NPs application for ascorbic acid delivery (AA) in (i) the rotifer *Brachionus plicatilis* in vivo and (ii) zebra fish liver cell line (ZFL). NPs were able to penetrate intestinal epithelium of fish and significantly increase AA on both models. Rotifers that fed with AA-NPs had up to twofold increase of their AA levels comparing to the control groups.

20.6.2 Growth Promotion

Zinc (Zn) is an essential micronutrient involved in many metabolic pathways, and Zn is essential for the protein synthesis regulation, consumption of energy as well as lipid and vitamin A metabolism (Muralisankar et al. 2014). Faiz et al. (2015) investigated nZnO as a dietary Zn source evidencing improved immune response and growth in grass carp (*Ctenopharyngodon idella*). Muralisankar et al. (2014) showed that weight, antioxidant enzyme activity, and protein content increased significantly in freshwater prawn (*Macrobrachium rosenbergii*) after feeding for 90 days with nZnO improved feed.

Bhattacharyya et al. (2015) reviewed the use of nanomaterials (NMs) for growth induction in aquatic species by increasing the nutrients' proportion passing through the gut tissue and so into the organism rather than that passing across the digestive system and then excreted partially or totally unused. Ramsden et al. (2009) used $nTiO_2$ to growth performance improvement in rainbow trout (*Oncorhynchus mykiss*).

Selenium (Se) is an essential trace element for life and recently has been considered for animal nutrition in many case studies (Polettini et al. 2015; Sabbioni et al. 2015). Se is glutathione peroxidase enzyme (GSH-Px) component (Rotruck et al. 1973), which maintains the cell membrane through reduction of glutathione. Se can be supplemented through diet (Wang et al. 2013; Ilham and Munilkumar 2016); moreover, Se NPs are gaining a great attention due to its antioxidant defense properties and bioavailability (Sonkusre et al. 2014). Prussian carp (*Carassius auratus gibelio*) fed nSe supplemented diets; results showed FCR reduction with increase in final weight, muscle protein content as well as liver and blood plasma GSH-Px activity (Zhou et al. 2009). Additionally, Wang et al. (2013) stated that nSe caused increase in LDH, GSH-Px, Na^+/K^+-ATPase, cellular protein contents, and superoxide dismutase (SOD) in crucian carp (*C. auratus gibelio*); moreover, these effects were related to both dose and NPs size. Deng and Cheng (2003) reported that nSe significantly improved Nile tilapia (*Oreochromis niloticus*) growth at moderate and high Se NPs doses (0.5 mg/kg), (2.5 mg/kg), respectively, via spiked feed presenting 86.3 ± 4.7 g weight gain rate.

20.6.3 Nano-encapsulation in Fish Feed

During the direct feed administration to water, feed nutrients can be released to water from feed pellets. These nutrients can easily degrade during contact with water. Chitosan NPs can be applied as an encapsulating agent (Chatterjee and Judeh 2016; Ji et al. 2015).

Essential oils (EOs) are volatile compounds and complex mixtures (mainly monoterpenes, benzenoids, and sesquiterpenoids, others) produced by different plant species like bushy matgrass (da Cunha et al. 2010; Becker et al. 2011), mentha (Danner et al. 2011; Roohi and Imanpoor 2015; Pedrazzani and Neto 2016), cloves (Perdikaris et al. 2010; Javahery et al. 2012), and others (Benovit et al. 2012; Parodi et al. 2013; Silva et al. 2015). Essential oils' (EOs) pharmacological properties include antioxidant, anti-inflammatory, and anticarcinogenic effects. Moreover, they have biocidal activity against many organisms such as bacteria, viruses, fungi, insects, and nematodes (Raut and Karuppayil 2014; Baser and Buchbauer 2015; Calo et al. 2015). In the aquaculture industry, EOs have great potential for use due to their attractive characteristics such as low cost, ready availability, low risk of side effects, low toxicity as well as high biodegradability comparing to antibiotic use and the risk of pathogen drug-resistant strain emergence challenge (Wei and Wee 2013; Anusha et al. 2014; Acar et al. 2015; Malheiros et al. 2016). EOs can also assist in the fish diets because they can improve the functioning and development of the digestive tract, especially in the early stages of fish development, preventing pathogen adherence to the intestinal mucosa, accelerating the glucose absorption, and stimulating the digestive enzyme secretion (Freccia et al.,2014; Hernandez et al. 2016; Zeppenfeld et al. 2016).

In aquaculture, anesthetics have been used to stress reduction in fish. Best anesthetic selection depends on several factors including availability, cost, physical conditions as well as the operative safety. Many anesthetics have not been used in aquaculture, due to toxicity and undesirable side effects (Zahl et al. 2011). As an alternative pathway, some essential oils have anesthetic activities in fish with greater biodegradability and reduced toxicity, compared to synthetic chemicals.

However, despite essential oils' (EOs) useful properties, some important limitations for aquaculture applications are present. Unfortunately, as in other aromatic and lipophilic compounds, EOs have low water solubility so their application in ponds, as well other aquatic media, is difficult. Other disadvantages of EOs are their high light sensitivity, low stability, and strong organoleptic characteristics, e.g., aroma and flavor (Turek and Stintzing 2013). Therefore, new approaches are required for EOs applications and nano-encapsulation is a technique that can improve their properties (Ghayempour and Montazer 2016).

Many studies of essential oil encapsulation by using several carrier systems, such as chitosan nanoparticles (Hosseini et al. 2013; Esmaeili and Asgari 2015; Hu et al. 2015; Mohammadi et al. 2015), zinc nanoparticles (Parris et al. 2005; Wu et al. 2012; Zhang et al. 2014a; da Rosa et al. 2015); cyclodextrins (Ciobanu et al. 2012; Hill et al. 2013; Siqueira-Lima et al. 2014; Abarca et al. 2016), polymeric nanoparticles (de Oliveira et al. 2014; Christofoli et al. 2015; Liakos et al. 2016); nanotubes (Lee and Park 2015; Kim et al. 2016); and solid lipid nanoparticles (Lai et al. 2006; Feng 2012; Moghimipour et al. 2013; Cortes-Rojas et al. 2014). Addition of single-walled nanotubes of carbon, C60, or nTiO_2 to rainbow trout food changed fish pellet physical properties and resulted in reduction of nutrients' leaching and their subsequent waste in fishpond (Ramsden et al. 2009).

20.7 Nanotechnology and Seafood

Fishing lures used to catch fish are painted to attract fish attention by light reflection. But conventional lures reflect light in one direction only. To overcome this problem, the lure surface is colored and then nanocoated with a polyimide film that enhances fish-catching chance 2–3 times comparing to a lure without using a polyimide coating. Before fish processing, Walha et al. (2008) applied the nanofiltration as well as reverse osmosis processes to reduce drilling water salinity

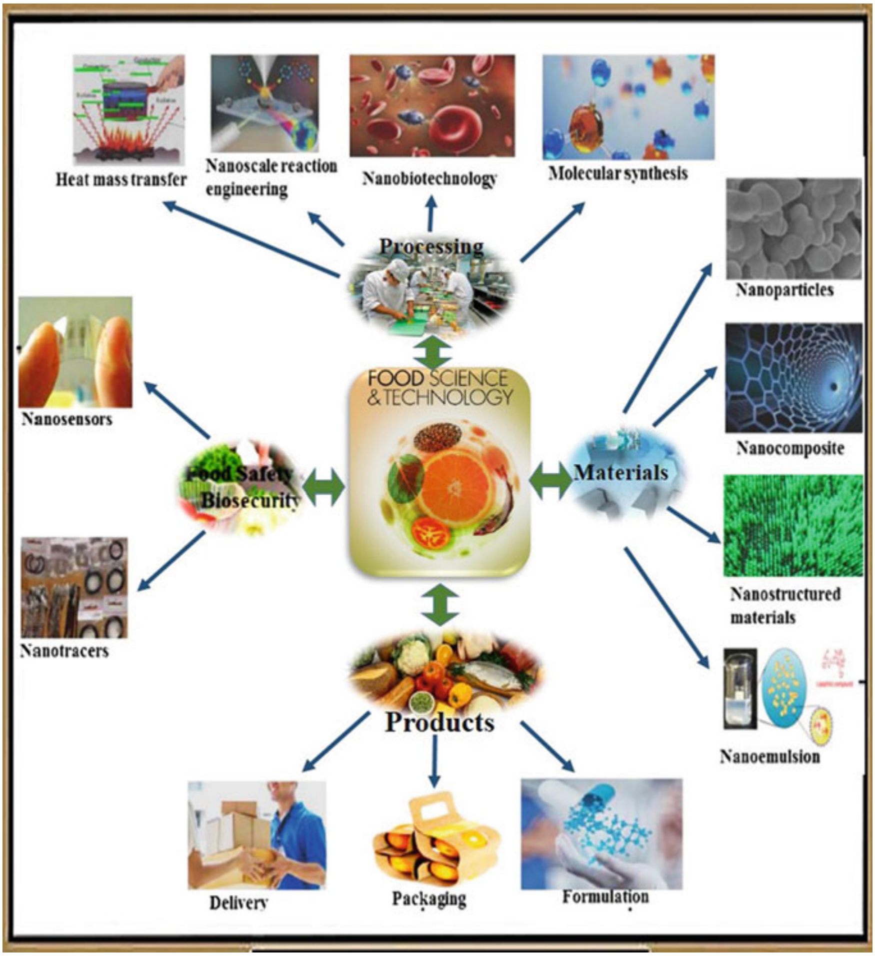

Fig. 20.11 Different steps of food management that involve several steps (processing, packaging, and preservation) and these aided by nanotechnology with the assistance of several nanomaterials. Redrawn from Thiruvengadam et al. (2018)

that is used in washing and processing of seafood. As pretreatment step, nanofiltration was used before the process of thermal and membrane seawater desalination.

Three different commercial ultrafiltration/nanofiltration (UF-NF) membranes XP117, MT03, and MT44 (cutoffs ranging between 200 and 4000 Da) are examined using a tangential flow filtration cell. The results detected that the MT03 membrane effectively removes the natural organic matter and reduces the concentration of sulfate in drilling water. Nanofiltration makes the water quality standardization possible (Fig. 20.11).

20.7.1 Harvested Fish Preservation and Packaging for Commercialization

Nanotechnology can have a vital role not only to fish production but also to the fishery product marketing, especially because of the widespread need to increase product shelf life. Hence, in the food packaging sector there have been great intensified research efforts (Omodara 2015).

Due to growing environmental concerns, the biopolymer use in the food industry has grown. However, this sector is still facing important problems related to the high costs of production and low performance, in comparison with synthetic polymers (Robertson 2016). Many scientific studies have shown that nanomaterial incorporation in biodegradable food packaging can improve the materials' thermal and mechanical properties and so can increase the performance.

Furthermore, new properties can be provided by nanomaterials, such as oxygen elimination, antimicrobial activities, antifungal activities, protection against degradation, and enzyme immobilization, hence contributing to stored products' better stability (de Azeredo 2009; Peelman et al. 2013; Rhim et al. 2013; Reig et al. 2014; Jiang et al. 2015; Kuswandi 2016). The whole nanoparticle use concept is based on their properties which are improved stability, penetrability, reactivity, surface area and strength, their mechanical, catalytic, optical, and quantum properties. The nanoparticles size allows their use in new or more efficient physical and chemical reactions comparing to larger-scale materials (Cockburn et al. 2012; Sastry et al. 2013; Ramachandraiah et al. 2015).

These useful properties will explain why nanotechnology should be implemented in food packaging. Nanopackaging can be classified to "improved" nanopackaging, which is used to improve the properties of packaging (e.g., mechanical and barrier properties); "active" nanopackaging, which allows interaction with the environment and food by absorbing or releasing substances from or into the packaged food; and "intelligent" or "smart" nanopackaging, which allows condition monitoring of the food surrounding environment or packaged food (Chaudhry and Castle 2011; Silvestre et al. 2011; Baltic et al. 2013; Prasad et al. 2017). Ramezani et al. (2015) studied chitosan and chitosan NPs effect on fillets of silver carp stored at 4 °C, and results showed that chitosan NPs had an interesting antimicrobial activity as well as inhibition ability of the total volatile nitrogen (TVB-N) content for improving a product general storage potentiality.

20.7.2 Nanobarcode and Tagging Technology

In our daily life, tags of identification have been applied in wholesale livestock and agriculture products. Due to nanoparticles' small size, nanoparticles have been used in many fields ranging from agricultural encoding to advanced biotechnology. Nanobarcodes (>million) have been applied in general encoding and multiplexed bioassays due to their ability to form a large combination number which make nanobarcodes attractive for this purpose.

The optical microscope and UV lamp are used for micrometer-sized glass barcode identification. These barcodes are formed by doping with rare earth containing different fluorescent material patterns of a specific type. The particles to be used in nanobarcodes should be machine-readable, durable, easily encodable, submicron-sized taggant particles.

For these nanobarcode particles' manufacture, the process is highly scalable and semiautomated, involving the inert metals (silver, gold, etc.) electroplating into templates defining particle diameter and then release of the resulting striped nanorods from templates. There are biological and non-biological applications for these nanobarcodes (Mathew et al. 2009). A major challenge for researchers is cost for nanobarcode technology development which can be concluded on the fact that only 18 documents are published on Scopus indexed article database (SIAD). Out of 18 articles, conference paper (six in number), notes (one in number), review article (two in number), and nine research articles were only available in last ten years by "nanobarcode" as keyword (SIAD 2014).

Similarly, with the same keyword only 32 articles are published in SciFinder® database. None of these articles were found for 2014; but only one article was found by Han et al. (2013). Similarly, three articles have been only found for 2012, but none of these articles have described nanobarcode application in agricultural field (SciFinder 2014). This shows that nanobarcode technology development for agricultural application is needed to be one of the thrust areas.

A nanobarcode is a monitoring device composed of metallic stripes containing nanoparticles as striping variations provide the encoding information method. By nanobarcoding incorporation, exporters and processing industry can monitor their aqua product source or track the delivery status until this product reaches the market. Further, coupled with nanosensors in addition to "synthetic DNA tagged with color-coded probes", nanobarcode device could monitor temperature change, detect pathogens, etc., thus improving the product quality.

Nanobarcodes have been utilized as ID tags for gene expression multiplexed analysis and intracellular histopathology. Plant resistance improvement could be achieved, against various environmental stresses as salinity, drought, diseases and others, through biotechnology advancement at the nanoscale. Soon, through nanotechnology advancement based on gene sequencing more effective utilization and identification of plant gene trait resources may introduce cost-effective and rapid capability (Branton et al. 2008). Nanobarcodes can also be used to detect pathogens from food products, and this is cost-effective (Han et al. 2013).

Nanobarcodes could also be used in many non-biological applications as - authentication or tracking in husbandry and agricultural food products. This technology will enable the development of new auto-ID technologies for item tagging that were previously not tagged with conventional barcodes (Branton et al. 2008). The entire chip can be nearly at a dust mite size—closer to microscale than nanoscale. Technology developers envision a world where any object anywhere can be automatically identified.

Radio-frequency identification (RFID) is “a chip with a radio circuit incorporating a nanoscale component with an identification code embedded in it”. These tag characteristics as can be scanned from a distance hold more information as well as identify any object, anywhere, automatically as they can be embedded in the product. RFID tag may be used in juvenile fish. RFID tag can be a tracking device and a device for monitoring fish swimming pattern, metabolism, and fish feeding behavior. Moreover, a possible benefit is to permit fish processing plants to identify fish source by incorporating the “nanobarcoding” as information management system part. This technology may also be used by exporters of the whole fish for tracking the delivery status of tagged fish. RFID nanotag advantages include memory storage capacity to product identification number, product cost, price, manufactured date, characteristics, and location as well as inventory on hand. The fresh food traceability, such as fish, has become an important challenging in order to keep consumer’s safety and freshness. Although this technology application on finfish aquaculture is yet to be studied, however the previously mentioned potential benefits could prompt industry participants for exploring this opportunity further (Rather et al. 2011a, b).

There are numerous bacterial diseases affecting humans such as tetanus, diphtheria, typhoid fever, cholera, syphilis, food-borne illness, tuberculosis, and leprosy caused by different bacterial species. As a remedial process, there is a need to detect bacteria, and so, dye staining method is used. For bacterial staining, organic dyes are the most commonly used biolabels, but their fluorescence degrades with time and they are expensive. So, there is a need to find economical and durable alternatives. Quantum dot fluorescent labeling with biorecognition molecules has been detected through the recent developments in luminescent nanocrystal field. Quantum dots are much better than conventional organic dyes because of their more efficient luminescence, excellent photostability, narrow emission spectra, tenability, and symmetry according to the sizes of particle and material composition.

By a single excitation light source, all colors quantum dots can be excited because of their broad absorption spectra (Warad et al. 2004). NPs biolabeled bacillus bacteria consist of ZnS and Mn^{+2} which capped with biocompatible “chitosan” that gave an orange glow when viewed by fluorescence microscope. For *E. coli* O157:H7 detection, quantum dots were utilized as a fluorescence marker that was coupled with immune magnetic separation (Su and Li 2004). For *E. coli* O157 detection, the magnetic beads were coated with anti-*E. coli* O157 antibodies for selective attachment to the target bacteria and with biotin-conjugated antibodies of anti-*E. coli* for sandwich immune complexes formation. Quantum dots were labeled by the immune complexes through biotin–streptavidin conjugation after the magnetic separation.

Another nanotechnology application possibility in seafood is using of different packaging and conservation techniques for providing food safety via delaying spoilage through enzymatic and microbial activities. Nanocomposite films are utilized mostly to foods with active/intelligent packaging (antimicrobial films) combination and edible film/coating technology. Nanocomposite films are formed from natural biopolymers, like polysaccharide, lipid, and protein. These sources are better packaging material than petrochemical-based plastics, and this is related to that they are environment-friendly, edible, and anticancerogenic (Dursun et al. 2010).

There are many studies that demonstrate the formulation potential based on biopolymers for using in aquaculture and the fishing industry (Borgogna et al. 2011; Alboofetileh et al. 2016; Joukar et al. 2017). Alishahi et al. (2014) reported the advantages of using chitosan-based nanocomposites in aquaculture and seafood industry; the usage of chitosan-based nanocomposites, as well as other

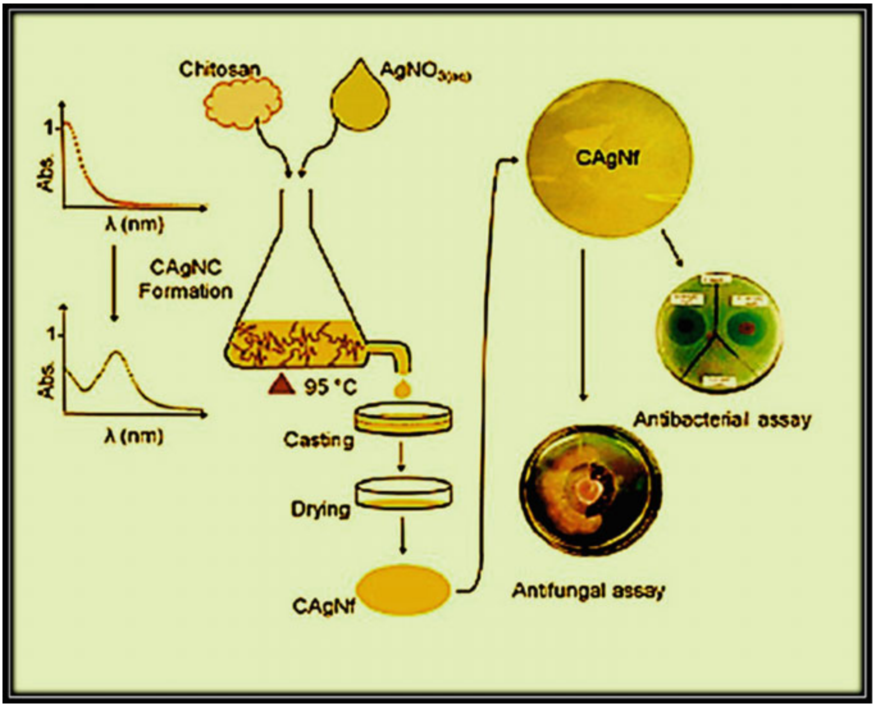

Fig. 20.12 Illustration of procedure for examining chitosan/$AgNO_3$ composites as antimicrobial film. Adopted Dananjaya et al. (2017)

biopolymers, could solve the problems faced in this sector, during a short-term period. Dananjaya et al. (2017) produced "silver nanoparticle (AgNP)-embedded chitosan films" that have antimicrobial properties. Results of antimicrobial experiment clearly detected that CAgNfs can inhibit the fish pathogenic bacteria growth such as *Vibrio tapetis*, *Vibrio* (Aliivibrio) *salmonicida*, and *E. tarda* and fungi growth such as *Fusarium oxysporum*. Moreover, CAgNfs significantly decreased the experimentally exposed levels of *V. salmonicida* in artificial seawater, and so there was a suggestion of using these CAgNfs to develop antimicrobial filters/ membranes to purify water units and eliminate the pathogenic microbes (Fig. 20.12).

The emulsion is the result of mixing two or more liquids which do not readily combine together such as water and oil (Ravichandran 2010). Nanoemulsions are "liquid-in-liquid dispersions with droplet sizes on the order of 100 nm". Nanoemulsions are highly stable in comparison with conventional emulsions. Moreover, nanoemulsions cannot be easily separated by using either gravitational forces or aggregation of the droplets due to the small size of the particle and droplets coating with surfactants that prevent the droplets from coalescing because of interfacial repulsion, respectively.

In the food industry, nanoemulsions are applied to ice creams, salad dressings, etc. With the small size particle, the products are creamier, are very easily transported through the digestive system epithelium, and therefore enhance the component adsorption better than other emulsions. Nanoemulsion has several activities against microorganisms either pathogenic or nonpathogenic (MNIMBS 2010). Nanoemulsions are commonly utilized for the phytochemical's delivery (Pradhan et al. 2015). Joe et al. (2011) tested the sunflower oil-based nanoemulsion (AUSN-4) influence on the quality and shelf life of steaks stored at 20 °C of Indo-Pacific king mackerel "*Scomberomorus guttatus*".

Among metal nanomaterials, Ag is the most promising one as it has both viricidal and bactericidal activities due to reactive oxygen species production that cleaves DNA as well as can be used for a wide range of applications in addition to other properties such as low toxicity, its charge capacity, ease of use, crystallographic structure, high surface-to-volume ratios, and adaptability to various substrates (Nangmenyi et al. 2009; Chen and Yada 2011; Faunce et al. 2014). Recently, researches have been tried to vary gold and silver nanoparticles' size with simple approaches, i.e., changing the reactant concentration. The improved anticancerous and antimicrobial activities were observed (Sireesh et al. 2015, 2017; Dasgupta et al. 2016a; Jain et al. 2016; Shukla et al. 2017; Siripireddy et al. 2017; Tammina et al. 2017). Recently, trends are changing in computational and silico as well as in vitro approaches for inorganic nanoparticle toxicity evaluation at biomolecular level (Ranjan et al. 2015, 2016a; Dasgupta et al. 2016b; Jain et al. 2016).

Fresh Box® is a developed antimicrobial container for food; it is produced by unique nanotechnology using fine polymers and shows tremendous properties against numerous fungi and bacteria due to its contents from finely dispersed Ag nanoparticles. Also, Rai and Bai (2018) reported a wide variety of "nanoproducts"

Fig. 20.13 Examples of some commercialized nanosilver-based products

achieved good sellers in markets, and these products contained metallic nanoparticles (Fig. 20.13).

20.7.3 Biosensors and Electronic Nose

Microorganisms produced various characteristic volatile compounds that are either useful or harmful to human beings; for example, yeasts' use makes fermentation while when bacteria eat sugar alcohol is produced as a by-product. Bacteria are the most common food rotting causal organisms. Foul odor is a clear indication of food degradation that may be detected by nasal and visual sensation; this sometimes may be impractical as well as for further causes of poisoning. Therefore, for these odors' detection it is more sensible to utilize an instrument as rapid detection biosensors (Compagnone et al. 1995).

The nano-biosensors' future applications were recently developed by Zhang et al. (2014b, c), in fields other than agriculture and food nano-biosensor area. Several sensors have been developed due to its importance; a review on this has been prepared by Rocha-Santos (2014).

20.7.3.1 Rapid Detection Biosensors

These instruments can reduce the time required for immunoassays and lengthy microbial testing. These instruments' applications include contaminant detection in different bodies such as food products, raw food materials, and water supplies (Compagnone et al. 1995). Recently, nano-biosensors are developed for IgG and metabolites' rapid detection (Turkoglu et al. 2013; Labroo and Cui 2014).

20.7.3.2 Enzymatic Biosensors

Enzymes are very specific for certain biomolecule attachment so they can act as a sensing element. According to Patel (2002), enzymatic biosensors on the immobilization surface basis are classified into controlled pore glass beads with optical transducer element, polyurethane foam with photothermal transducer element, ion-selective membrane with either potentiometric or amperometric transducer element, screen-printed electrode with amperometric transducer element. Regarding microbial contamination, an electrogenerated chemiluminescence immunosensor was developed to detect *Bacillus thuringiensis* using Fe_3O_4-Au nanoparticles (Li et al. 2013). An optical fiber-based micro-analyzer in aquaculture was used to measure fish volatile amine levels. This has future aspect for developing such nano-biosensor instead of micro (Silva et al. 2010).

Electronic nose is an instrument based on the human nose operation and is applied for odors' different types of identification; electronic nose uses a response pattern across a gas sensor array. Electronic nose can identify the odorant, find the odor characteristic properties, and estimate the odorant concentration in the same way as that of the human nose. It is mainly composed of gas sensors which consist of nanoparticles and ZnO nanowires, for example (Hossain et al. 2005; Sugunan et al. 2005). ZnO nanorods are utilized to develop electronic nose that can detect the impurities from vapor mixture (Ko et al. 2013). Their resistance changes with certain gas passage and generates a characteristic change in electrical signal which forms the fingerprint pattern for detection of gas. This pattern is applied to determine the type, quantity, and quality of the detected odor. An improved surface area is also present that helps in better gas absorption.

20.8 Safety Concerns of Nanotechnology in Aquaculture

Nanotechnology use can revolutionize the aquaculture industry (Fig. 20.13), but further research is still a vital need for an effective and viable commercial implementation of this technology (Fig. 20.14). Some of the main problems which should be addressed are cost analysis, the scalability of these systems, and the possible environmental impacts (Fig. 20.15). Aquaculture and fishery industries

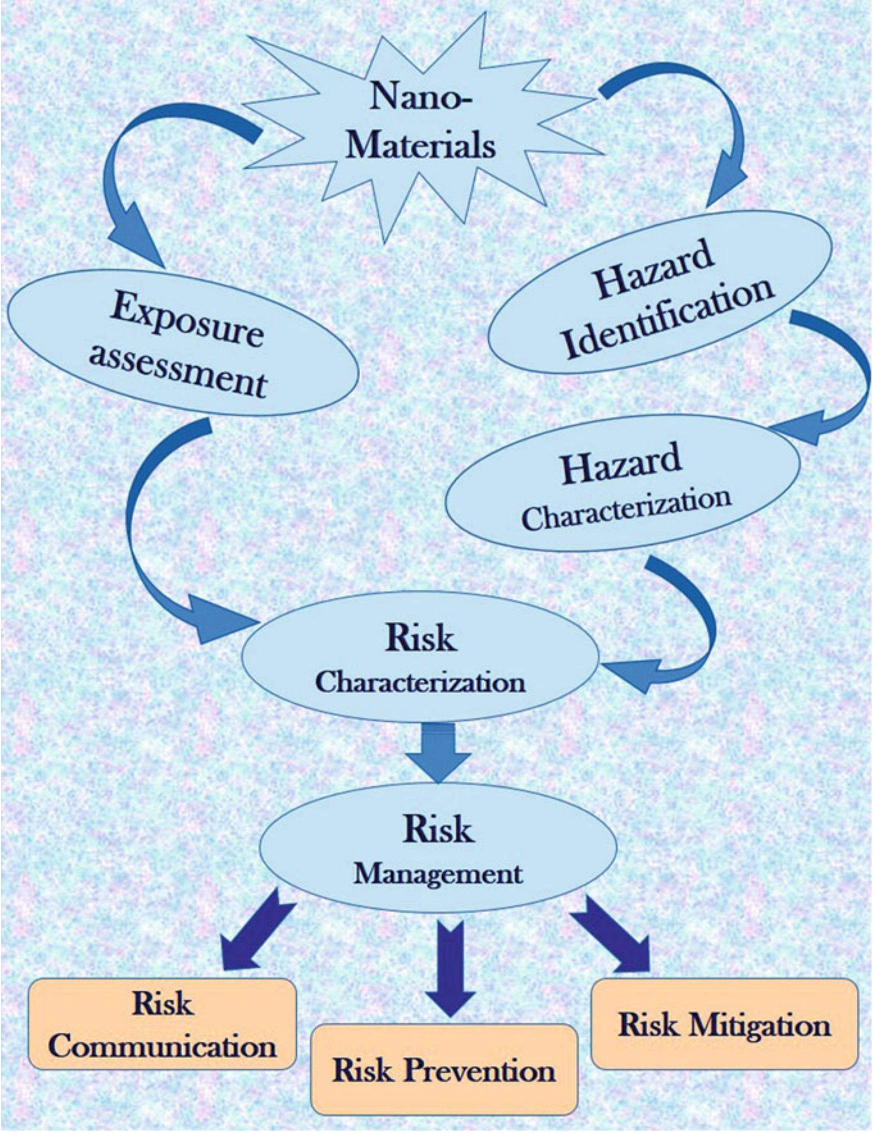

Fig. 20.14 Toxicological aspect of nanomaterials on humans, animals, environment, and whole ecosystem. Diagrammatic representation of nanotoxicological analysis. Redrawn after Dasgupta et al. (2017)

will have to absorb the new technologies to move forward. Moreover, safe use and the rational of nanotechnology will contribute to progress.

When it comes to nanotechnology application in the industrial scale, it is very important to estimate the subsequent exposure levels to these materials and to

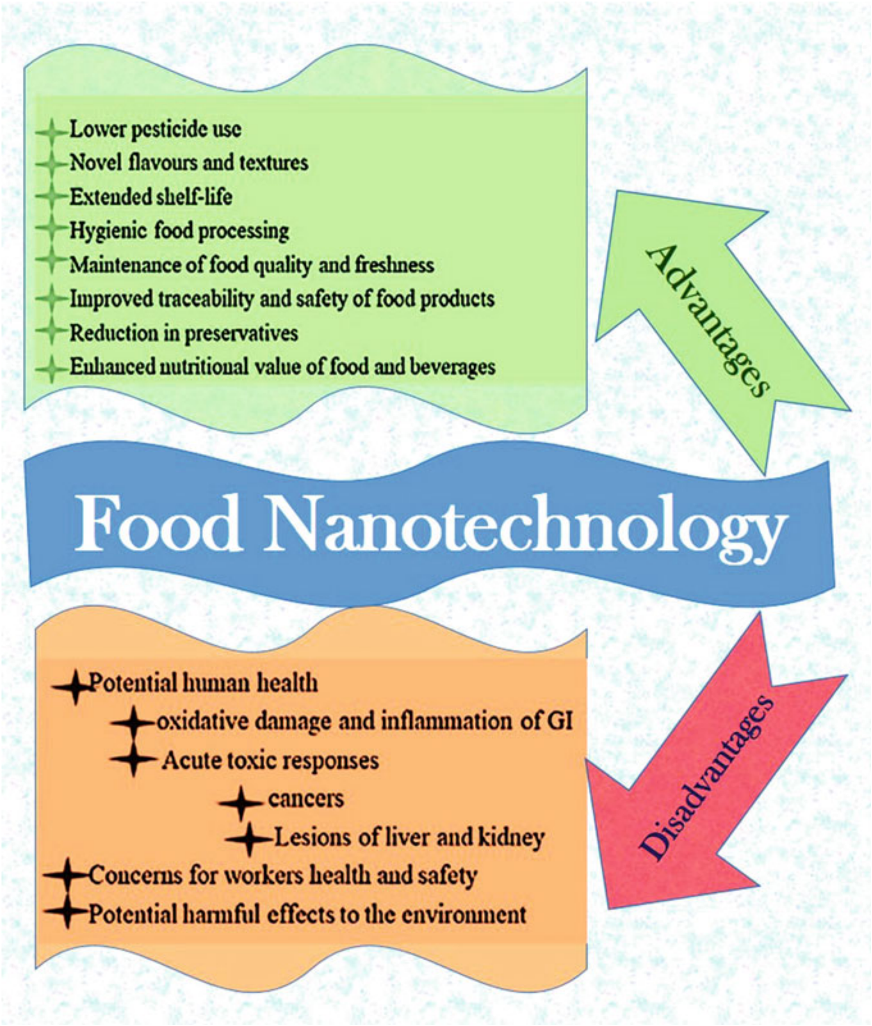

Fig. 20.15 Benefits and risks of nanotechnology applications in food and related products. Redrawn from Thiruvengadam et al. (2018)

evaluate nanoparticle release into the environment because nanoparticles can easily penetrate organ and organelles of the human, so exposure concentrations, exposure time, immune response, sites of penetration as well as nanoparticle retention and accumulation in body and so their subsequent effects should be evaluated carefully.

Even though the research regarding nanotechnology application is growing every day, in the naturally occurring nanosystems still insufficient scientific examination is available. Treated water and/or nanomodified agricultural products' compulsory testing should be performed before they are introduced into the market.

Standardized test procedures are required for studying nanoparticle impacts on living cells to evaluate the risks on human exposed to nanoparticles. Nanoparticle toxicology is poorly understood due to the lack of validated test methods as well as the inconsistency in the reported information. The inconsistency in the reported data is related to nanoparticles' improper characterization and the nanoparticle interferences in the available test system.

Hence, the policy makers and the regulatory bodies should provide the guidance document to safe uses, the validated protocols, and the nanoparticle disposal. The understanding of the nanoscience and nanotechnology safe application in water quality management and agri-food will help in the "nano-agri-technology" sustainable growth. Regulatory and government authorities (regulatory agencies and certification bodies) as well as health, environmental, and safety councils (such as environmental health services), scientific authorities, and non-governmental organizations, all over the world, detected the nanotechnologies' risk assessment importance (Vyom et al. 2012) and have given their own view, suggestion, and guidance (RS/RAE 2004; USEPA 2007; SCCP 2007; Scenihr 2009; Dhawan et al. 2011). The same nanomaterial, with a different length, diameter, surface modification, and crystal structure, will have different toxicities (Fig. 20.14).

20.8.1 Effects of Nanotechnologies on Human Health

There are four pathways where nanoparticle may enter the body of human: swallowing, inhalation, skin absorption, and deliberate injection during medical processes (or release from implants). Due to the fact that nanoparticle diameter is extremely small, once these nanoparticles have entered the human body, nanoparticles have a high mobility degree. So they can pass the blood-brain barrier in some cases.

The potential nanoparticles danger to human and animals do not allow neglect. University of Missouri (USA) researchers detected in their recent study nanoparticle residue in fruits can enter the human body. So, it also can get into the liver, spleen, heart, brain, etc., vitals, through lymphatic and blood system. It was demonstrated that the residue of nanoparticle is very difficult to be removed by common rinsing methods. Therefore, they appeal that in food wrap papers, nanotechnologies should be carefully used.

20.8.2 Effects of Nanotechnologies on Fish Health and Aquatic Environment

The nanoparticle toxicity has focused in mammalian models on the respiratory exposure and the human health implications (Handy and Shaw 2007). With the nanotechnology's rapid development, there is an increasing risk for human and environmental exposure to the nanotechnology-based materials and products. Water resources are particularly vulnerable by nanotechnologies' direct and indirect contamination, and the nanotechnologies' environmental implication and potential toxicity to aquatic organisms must be evaluated (Wang et al. 2008). TiO_2 nanoparticle suspension stability in water had been investigated (Hao et al. 2009). One hundred and 200 mg/L TiO_2 nanoparticle resulted in statistically significant reduction in superoxide dismutase (SOD), peroxidase (POD), and catalase (CAT) activities and significant increase in levels of lipid peroxidation (LPO) in tissues, suggesting that fish exposed to TiO_2 nanoparticles two concentrations suffered from the oxidative stress.

A comprehensive toxicity assessment included the modified acute (72 h) as well as the chronic (21 days) toxicity tests, and accumulation analysis of TiO_2 nanoparticles using a model organism such as *Daphnia magna* was conducted (Zhu et al. 2010a, b). The results showed that TiO_2 nanoparticle within the traditional 48-h exposure time exerted minimal toxicity to daphnia, but when the time of the exposure was extended to 72 h TiO_2 nanoparticle caused high toxicity. This demonstrates that the duration of the exposure may be a contributing factor in mediated toxicity of nanoparticle. Moreover, upon TiO_2 nanoparticles' chronic exposure for 21 days, daphnia displayed severe mortality and growth retardation in addition to reproductive defects. TiO_2 nanoparticle and quantum dot potential toxicity using the unicellular green alga "*Chlamydomonas reinhardtii*" were assessed (Wang et al. 2008).

The growth kinetics showed that inhibition of growth occurred in the first two to three days of cultivation in TiO_2 nanoparticle or quantum dots' presence. Moreover, quantum dots were more toxic than TiO_2 nanoparticle to Chlamydomonas cells under experimental conditions. These results indicate a potential risk of TiO_2 nanoparticle released to the aquatic environment. The different aqueous nanotechnology suspensions, such as nZnO, $nTiO_2$, C_{60}, nAl_2O_3, single-walled carbon nanotubes, and multi-walled carbon nanotubes, can inhibit the algae growth *Scenedesmus obliquus* (*S. obliquus*) as well as prevent movements of *D. magna* and can lead to death. However, several nanomaterial toxicities are not similar to each other (Wang et al. 2008).

According to six types of nanomaterial EC values on *S. obliquus* growth at 96 h, the toxicity order was as follows: "nZnO > C60; TiO_2, multi-walled carbon nanotubes and single-walled carbon nanotubes > nAl_2O_3". While according to the EC values on *D. magna* movement inhibition at 48 h, the toxicities order of the nanomaterials aqueous suspensions of six types were as follows: "nZnO > single-walled carbon nanotubes > C60; multi-walled carbon nanotubes > $nTiO_2$ > nAl_2O_3".

The effects of Ag nanoparticle's different particle sizes (61, 25, and 5 nm) on growth of ryegrass, biomass, and seedling height were investigated (Yin et al. 2011); the smaller the size of the nanoparticle, the stronger its toxicity was. Yang et al. (2010) investigated single-walled carbon nanotubes' different lengths of

(<l, 1–5, and 5 m) effects on the bacteria inhibition such as *Salmonella typhimurium,* and results showed that the single-walled carbon nanotubes' antibacterial ability increased with the increase in their lengths.

Khosravi-Katuli et al. (2017) summarized the various NPs information in addition to the target organisms of aquaculture interest and the main relative testing conditions. However, in the aquaculture industry there may be some concerns about development activities and research, for example, in situations where researchers were preparing new NMs containing feed formulations in the laboratory. The occupational exposure to NMs at the laboratory has been investigated (Demou et al. 2009; Tsai et al. 2009). The evidence suggests the routine procedures with manufactured NMs few grams, such as stirring and sonication, when normal precautions are applied in the laboratory (e.g., gloves, use of a ventilated fume cupboard, or a suitable dust mask).

It is worthy to mention that for routine research activities the normal precautions in the laboratory should be followed but personal protective clothing will not be needed, but of course, "researchers are required to carry out chemical risk assessments for NMs before they start work, as with any other laboratory procedure".

Surface inputs could be atmospheric deposition and coastal pollution. The seawater pH (typically pH 8) and, moreover, high ionic strength will enhance aggregation processes, so NPs may precipitate onto either coastal or deep ocean sediments (Fig. 20.16). However, with depth chemistry will change. Diatoms and

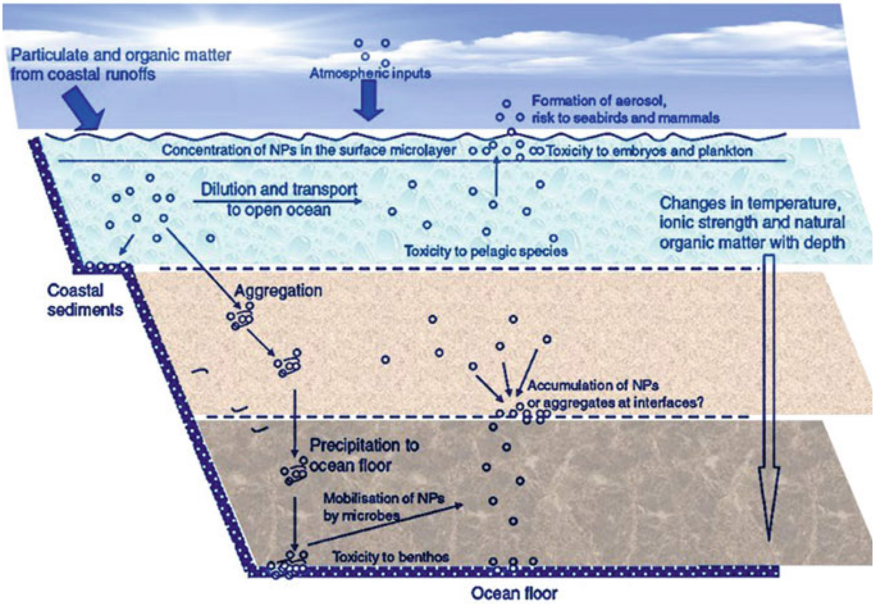

Fig. 20.16 Schematic diagram outlining the possible fate of nanoparticles (NPs) in the marine environment and the organisms at risk of exposure. Redrawn from Klaine et al. (2008)

microbes can remobilize the accumulated NPs on/in sediments. It is unclear whether NPs will accumulate in the ocean current mixing zones, there is a risk to organisms which feed at these interfaces. Some manufactured NPs may have surface activities that permit them to still disperse in saline conditions, and these NPs could accumulate because of surface tension effects and viscous properties at the ocean surface microlayer with consequent risks for planktonic organisms and larvae in the surface microlayer.

Ecotoxicity information so far suggests low acute toxicity by manufactured NMs to aquatic species, and so aquaculture systems and fisheries' immediate threats may be very small. However, on low-level exposure chronic studies are needed using realistic environmental scenarios to determine nanotechnology long-term impact on the environment, which must be balanced against nanotechnology benefits in water purification and environmental remediation technologies.

The NMs behavior and colloid chemistry suggest that NMs are likely to be precipitated in the water column and this will be particularly associated with sediments underneath fish cages. However, for the industry, this is not a new issue, and aquaculture systems under caged benthic environments are monitored for biodiversity and pollution (Carroll et al. 2003). Public engagement will be important to maintaining confidence in nanotechnology, especially with respect to the environment and food safety. Overall, nanotechnology benefits are worth pursuing in aquaculture so the hazard to wildlife should not act as a barrier to innovative, responsible "aqua-nanotechnology" development.

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Part IV
Nanomaterials in Food and Food Safety

Chapter 21
Application of Nanotechnology in Functional Foods

Richa Singh, Bimlesh Mann, Rajan Sharma and Sulaxana Singh

Abstract In food application, encapsulation is a technique in which the functional ingredient is packed inside a protective coating to prevent from chemical or biological degradation during processing, storage, and utilization. Depending upon the size of encapsulated product, it can be termed as micro-encapsulation or nano-encapsulation. The smaller size of nano-encapsulation offers benefits like micro-encapsulation but in better way. Nano-encapsulation provides protection to sensitive bioactive ingredients which then can be added into food products, and it helps in masking off taste and prevents unnecessary interactions with other constituents. It also improves solubility of poorly water-soluble ingredients. Nano-encapsulation enhances the bioavailability of functional ingredients as they are designed in such a way that they protect digestion of bioactive ingredients in stomach and ensure release of food ingredients at a site of action for optimal uptake. Therefore, nanotechnology has great potential for improving the effectiveness and efficiency of delivery of nutraceuticals and bioactive compounds in functional foods to improve human health. However, the nano size is associated with the risk as it can cross the cell barrier. At present, there is no nano-specific guidelines, guidance documents for testing, or testing requirements under any of the existing regulations that relate specifically to nanoparticles in terms of size or other distinct physico-chemical properties which may pose a major barrier in commercialization of nano-encapsulated food products.

Keywords Functional food · Nutraceuticals · Nano-encapsulation · Bioactive compounds · Characterization

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21.1 Introduction

Nowadays, the demand of food products providing health benefits is increasing, as consumers are becoming more aware about the impact of diet on their health. Therefore, the addition of health-promoting ingredients like vitamins, minerals, essential fatty acids, carotenoids, antioxidants, phytosterol, and fibres has been gaining considerable interest in the form of functional foods (Aboalnaja et al. 2016; McClements 2013; Prasad et al. 2014; Zou et al. 2015). However, the addition of these ingredients into food formulation is a challenging task because these are unstable during processing and storage of food due to their rapid degradation (oxidation or hydrolysis) triggered by different environmental conditions (temperature, pH light, oxygen, moisture, etc.) and they can undergo different undesirable interaction with other food components. Some bioactive materials (polyphenols, peptides, phytochemicals, etc.) also possess unpleasant aroma and flavour that can impart unpleasant taste and astringency. These bioactive compounds are unstable during their passage through gastrointestinal tract (GIT) in the presence of varied pH range and the presence of enzymes and therefore sometimes get degraded in the stomach itself before reaching to small intestine resulting in lower bioavailability. Some bioactives (curcumin, essential oils, bioactive lipids, etc.) are poorly soluble in aqueous solution that limits their application in functional foods (McClements and Li 2010; Sousa et al. 2014; Zhu et al. 2015). According to FDA, the bioavailability of ingredient is defined how much concentration of added ingredient is being absorbed in the GIT and available at the site of action (Pathak and Raghuvanshi 2015). Poor bioavailability of bioactive ingredient is due to poor solubility, chemical instability as well as ingredient interaction with other food components (McClements 2013). Nano-encapsulation of these heat and oxygen sensitive bioactive compounds may be a potential approach for their incorporation into functional foods. Because it preserves them during processing and storage, mask unpleasant tastes and flavours, make them water dispersible, control their release and hence improves bioavailability (Aboalnaja et al. 2016; Jafari and McClements 2017). Nanotechnology is a multidisciplinary approach (physics, chemistry, biology, biotechnology, engineering, etc.) that deals with preparation and application of nano-sized (1–100 nm) ingredient. While, in the food system, most of the micro-encapsulated products have diameters between 1 and 1000 μm (Umer et al. 2011), nano-encapsulated products have diameters less than 1000 nm (Sanguansri and Augustin 2006). Nanotechnology is one of the emerging techniques, in which particle size decreases to nanoscale range which increases surface-to-volume ratio and consequently change in their reactivity including change in mechanical, electrical, and optical properties that is applied in medicines, cosmetics, agriculture, and food sector (Neethirajan and Jayas 2011).

The nanotechnology has already been utilized in the area of medical, computer electronics, communications, energy production field, etc. However, the use of nanotechnology in food industries was first addressed by road map given by US

Department of Agriculture (USDA) published in September 2003 (Joseph and Morrison 2006). Different biomolecules like casein micelles and fat globules network already exist as nanoparticles in milk system. However, the food nanotechnology describes engineered nanoparticles which have been added in food. The nanoscale material possesses the novel properties and hence offers great potential in food industries, especially for the development of functional foods. Different types of functional nanostructured components can be utilized as building blocks to develop novel structure and to introduce the new functionalities to the food products. Several nanoscale materials can be utilized in functional foods such as nanocapsules, nano-emulsion, liposomes, nanofibers, nanotubes, etc. Both organic and inorganic nanomaterial can be used in the food applications (Chaudhry et al. 2008).

21.2 Production of Nanoparticles Enclosing Bioactives

There are two approaches for formation of nanoparticles such as top-down and bottom-up approaches. In the top-down approach (techniques used: emulsification, solvent evaporation, and high-pressure homogenization), the nanonization is achieved by the application of energy to break bulk materials that allows size reduction and structure shaping for particular application, while bottom-up approach (techniques used: coacervation, nanoprecipitation, inclusion complexation, and supercritical fluid) involves the building of nanoparticles from individual atoms that have the ability to self-assemble in a natural and self-regulating manner (Paredes et al. 2016). Both approaches are fundamentally different. The rate of production is lower in top-down approach, and bottom-up approach results in more homogenous chemical composition compared to top-down approach (Hsieh and Ofori 2007).

In nano-encapsulation, the bioactive compound acts as core material and needs to be covered with a wall material that is known as coat. Each core material is different in terms of polarity, solubility, molecular weight, and the physical state, and thus, the interaction between the core and the coat material affects the functionality of nanoparticles. Therefore, each core material needs to be incorporated within a suitable wall material. For food application, the carrier material needs to be food grade, having GRAS ("generally regarded as safe") status and biodegradable in nature (Nallamuthu et al. 2017). The most commonly used wall materials include carbohydrate, lipid, and protein. Under carbohydrate, commonly used ingredients are alginate, starch, dextrin, chitosan, guar gum, xanthan gum, pectin, galactomannan, cellulose, and their derivatives (Fathi et al. 2014; Kim et al. 2013). In lipid category, egg yolk phospholipid, phosphatidylcholine, cholesterol, medium- and low-chain triglyceride, lecithin, soybean oil, corn oil, and olive oil are being used (Shin et al. 2015). In protein category, gelatine, whey proteins, sodium caseinate, zein, and soy proteins are used (Guri and Corredig 2014; Joye et al. 2015; Patel and Velikov 2014; Ramos et al. 2014; Shpigelman et al. 2014; Tavares et al. 2014).

Different methods are used for production of nano-encapsulated bioactive ingredient. The first technique is coacervation, in which phase separation of polyelectrolytes (single or mixture) from a solution is achieved, which subsequently gets deposited around bioactive ingredient to form a coat. The colloid so formed is called as coacervate. Various agents can be used to achieve phase separation such as salt, temperature, pH, or by anion–cation interaction. In simple coacervation, only one type of polyelectrolyte is used, and in complex coacervation, two or more types of polyelectrolytes are used. Sometimes agents like glutaraldehyde or transglutaminase are used for cross-linking of hydrocolloid to increase the robustness of the coacervate (Zuidam and Shimoni 2010). This technique is used for encapsulation of both hydrophilic and lipophilic compounds. Xing et al. (2005) used complex coacervation technique for nano-encapsulation of capsaicin (a pungent ingredient of pepper) that has an antimicrobial activity against food-borne pathogenic bacteria (*Staphylococcus aureus, Listeria monocytogenes, Bacillus cereus,* etc.). Lv et al. (2014) prepared heat-resistant nanocapsules of jasmine essential oil by using complex coacervation technique. Gan and Wang (2007) prepared nano-encapsulated bovine serum albumin (BSA) for its controlled release.

Second simple and reproducible technique is nanoprecipitation that is mostly used for encapsulation of lipophilic bioactive compounds. This method is also called solvent displacement. In this technique, two miscible phases, water phase and oil phase (organic solvent like ethanol/acetone, polymer, and bioactive compound), are stirred together on magnetic stirrer. The organic solvent is diffused in the aqueous medium (Galindo-Rodriguez et al. 2004), and due to the difference in surface tension of both phases, vortices of solvent are formed at interphase of liquids. This causes precipitation of polymer on oil phase and formation of nanoparticles. Biodegradable polymers like polycaprolactone (PCL), poly-lactide (PLA), poly-lactide-co-glicolide (PLGA), and poly-alkyl cyanoacrylate (PACA) are used in nanoprecipitation (Ezhilarasi et al. 2013; Reis et al. 2017). de Sousa Lobato et al. (2013) used nanoprecipitation technique for bixin, which is having poor water solubility that impairs its use in low-fat foods. Mitri et al. (2011) prepared lutein nanocrystals to overcome the problems of poor water solubility and low bioavailability for its oral delivery. Zein–curcumin nanoparticles were also synthesized using precipitation method (Patel et al. 2010). In another study, nanoparticles of poorly water-soluble antioxidant bioactive compound curcumin were prepared (Kakran et al. 2012). Chu et al. (2007) and Ribeiro et al. (2008) prepared nanoparticles of β-carotene stabilized by different types of milk proteins or by a blend of surfactants (Tween 20) and surface-active polymers (gelatin, PLA, and PGLA). Suwannateep et al. (2011) prepared nano-encapsulated curcumin for improving its oral bioavailability and sustainability. Inclusion complexation technique is also used for encapsulation of lipophilic compounds like volatile organic molecules (essential oils and vitamins) and is useful to mask odours and flavours and to preserve aromas. In this method, encapsulated ingredient (e.g. β-cyclodextrin and β-lactoglobulin) is complexed with wall material through hydrogen bonding, van der Waals force, or hydrophobic bonding. This technique yielded higher encapsulation efficiency with higher stability (Ezhilarasi et al. 2013). Zimet and Livney (2009) used nanocapsules of docosahexaenoic acid (DHA) prepared by inclusion complexation method to improve its colloidal stability and provide protection against degradation during its incorporation in acid drink. In supercritical antisolvent precipitation technique, supercritical carbon dioxide (CO_2) is used as a solvent that behaves as supercritical fluid above its critical temperature and pressure (31 °C and 73.8 bar) and possess properties of both liquid (density) and gas (viscosity). In this process, solute is first dissolved into an organic solvent followed by its mixing with supercritical $CO_{2.}$ As under these conditions, organic solvent and supercritical fluid are highly miscible, this leads to precipitation of solute in nano size (Clark 2009). This technique has been widely used because of its low critical temperature and minimum use of organic solvent. Heyang et al. (2009) prepared lutein nanoparticles to improve its bioactivity and to avoid its thermal/light degradation for its promotion as food ingredient. Türk and Lietzow (2004) prepared nanoparticles of phytosterol using supercritical CO_2 with improved solubility and bioavailability. Nerome et al. (2013) prepared lycopene/β-cyclodextrin nanoparticles using CO_2 as a supercritical antisolvent. Hu et al. (2012) prepared and characterized lutein/zein nanoparticles prepared by supercritical fluids to protect it from light degradation and improve its aqueous solubility as it has been reported that it may decrease the risk of age-related macular degeneration (Ma and Lin 2010; Stringham et al. 2010; Van Der Veen et al. 2009).

Emulsification is most commonly used technique for encapsulation of bioactive ingredient. In the emulsion preparation, two immiscible liquids are mixed together in the presence of a surfactant as interface agent. Nano-emulsions may be in different forms like single oil-in-water (O/W) or water-in-oil (W/O) nano-emulsions or in double nano-emulsions (O/W/O or W/O/W (Akhavan et al. 2018; Jafari et al. 2017). Oil-in-water emulsion is used for the encapsulation of hydrophobic bioactive compounds (curcumin, essential oil, etc.), and water-in-oil emulsion is used to encapsulate hydrophilic compounds (polyphenols). Bioactive compounds which have very limited solubility in water can be encapsulated by this technique for their incorporation in functional foods and pharmaceutical applications (McClements and Li 2010). High-energy emulsification and low-energy emulsification are two approaches that are used for preparation of nano-emulsions. The high-energy emulsification is achieved by use of mechanical energy using high shear blending, high-pressure homogenization, ultrasonication, and microfluidization techniques. The low-energy emulsification is achieved by the use of chemical energy using phase inversion technique, phase inversion temperature, and solvent demixing technique. (Abdullaeva 2017). Mayer et al. (2013) produced nano-emulsions enriched with vitamin E. Kumar Dey et al. (2012) compared the intestinal absorption of fish oil in nano- and conventional emulsion formulations and demonstrating the superior absorption of nano-encapsulated oil. Liang et al. (2013) and Pinheiro et al. (2013) used high-speed homogenization for preparation of nano-emulsion of β-carotene and curcumin, respectively. Salvia-Trujillo et al.

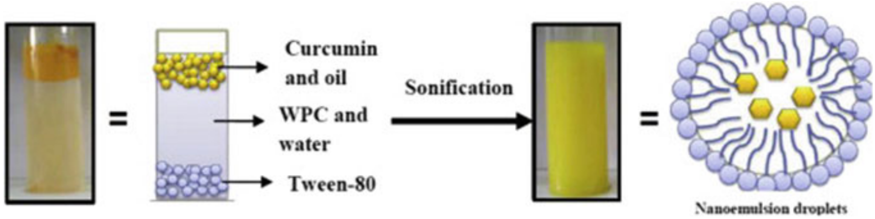

Fig. 21.1 Nano-emulsion encapsulating curcumin (Sari et al. 2015)

(2015) used high-pressure microfluidizer for preparation of nano-emulsion of β-carotene. Sunflower oil nano-emulsions prepared by ultrasonication method were evaluated for its stability (Shamsara et al. 2015). Shahavi et al. (2015) prepared clove oil nano-emulsions with less than 50 nm droplet size using ultrasonication. Su and Zhong (2016) investigated lemon oil nano-emulsions, prepared by phase inversion temperature using combinations of Tween 20 and sodium caseinate. Sari et al. (2015) encapsulated curcumin in medium-chain triglyceride oil droplets of nano-emulsion prepared by ultrasonification using whey protein concentrate-70 and Tween-80 as emulsifiers (Fig. 21.1). Sharma et al. (2017) prepared clove oil nano-emulsions by high-speed homogenization technique using sodium caseinate and pectin as coating material. Sonu et al. (2018) prepared D-limonene oil nano-emulsion stabilized by whey protein–maltodextrin conjugates using ultrasonication.

21.3 Bioavailability and Release Kinetics of Nano-encapsulated Bioactive Ingredient

On uptake, a nutrient must pass through the GIT for its final absorption at the site of action. The process in GIT can be divided into three phases: oral processing, gastric phase, and intestine phase. During the oral processing, the food is mixed with saliva and broken down into smaller particles and passed to stomach. In stomach, due to highly acidic conditions and the presence of enzymes (pepsin), the food undergoes different physical and chemical reactions. The digestive food enters into small intestine and is absorbed through active and passive transport system. Nano-encapsulation provides protection to bioactive ingredient against degradation in acidic and alkaline conditions, and their small size will help in higher uptake and absorption (Acosta 2009) due to controlled release of bioactive ingredient at its target sites (Mozafari et al. 2007). The delayed and sustained releases are the two mechanisms for controlled release of bioactive compounds. In delayed release, the bioactive ingredient is protected in gastric phase and released in the intestinal phase; however, in sustained release, concentration of bioactive ingredient is maintained over an extended release time (Fathi et al. 2012). There are different factors such as type, shape, and dimension of carrier that affect the release of nano-encapsulated bioactive ingredient (McClements and Li 2010). Therefore, the designing of nano-encapsulation is an important parameter that can affect the bioavailability of encapsulated ingredient. Different workers have reported higher bioavailability of nano-encapsulated bioactive ingredients using in vivo models. Penalva et al. (2015) reported twofold higher bioavailability of folic acid encapsulated in zein nanoparticles compared to its free form. Chaurasia et al. (2015) reported higher bioavailability of curcumin in phosphatidylcholine-maltodextrin-based nanoparticles. Kamil et al. (2016) reported increased pharmacokinetic parameters in PLGA nanoparticle encapsulating lutein compared to its free form. Faisal et al. (2013) reported 2.4-fold higher bioavailability of lycopene in lipid-based solid dispersion in pig model. Pandita et al. (2014) reported eightfold higher bioavailability of resveratrol in solid nanoparticles than suspension. Sari et al. (2015) prepared nano-encapsulated curcumin in medium-chain triglyceride oil droplets of using whey protein concentrate-70 and Tween-80 and studied the release mechanism of curcumin under simulated GI conditions and reported that the curcumin nano-emulsions were relatively resistant to pepsin digestion but released curcumin on action of pancreatin in intestine. That delayed release was supposed to increase bioavailability of curcumin. Kumar et al. (2016) studied release kinetics of curcumin nano-emulsions using simulated gastrointestinal digestion and suggested that the nano-emulsion was stable against pepsin digestion (only 5.25% release of curcumin), while pancreatin action led to a 16.12% release of curcumin from the nano-emulsion.

21.4 Application of Nanotechnology as a Delivery System in Food Products

The application of nanotechnology in food involves either the processing of ingredient to form nanostructure or addition of nano-encapsulated additives in food (Chaudhry et al. 2008) (Table 21.1). Nano-emulsions, double or multiple emulsions are examples of nanostructured food products (Weiss et al. 2006) used in foodstuffs like spreads, mayonnaise, cream, yoghurts, ice creams, etc., to improve tastes, textures, and consistency. For example, a low-fat nanotextured food product that is as “creamy” may be used as a healthy alternate to full fat. However, the much-exploited application of nanotechnology is encapsulation of bioactive compounds (minerals, antimicrobials, vitamins, antioxidants, etc.) for improved stability, absorption, and bioavailability for better dispersion, and bioavailability for formulation of health foods, supplements, and nutraceuticals. Nano-encapsulation is the technological extension of micro-encapsulation and offers similar benefits in better way, in which, the sensitive and bioactive substances are coated within an inert material so that they can reach to their target site without degradation by environmental and processing factors (Weiss et al. 2006). Depending upon the size of encapsulated product, it can be termed as micro-encapsulation or

Table 21.1 Different functional foods added with nano-encapsulated bioactive ingredients available in international market (Momin et al. 2013; Ramachandraiah et al. 2015)

Nano-encapsulated	Size (nm)	Function	Products	Manufacturer
Nano-emulsion (o/w)	50–500	Nano-encapsulation and regulated release of bioactive compound	Beta carotene, vitamin E nano-emulsion-based ice cream	Nestle, Switzerland; Unilever, UK
Biopolymeric nanoparticles	100	As a nutraceutical, antimicrobial agents,	Beta lactoglobulin nanoceuticals	RBC Life Science, USA
			Nano calcium/magnesium	MAG-I-CAL.com USA
			Selenium-enriched nanotea	Shenzhen Become Industry, China
Nanocapsules-vesicles	20–100	Improved solubility and addition levels	Nanocapsules of capsicum, oleoresin, eugenol, lysozymes, vitamins, phytosterols Tip Top bread with nanofish oil	Nu-Mega Driphorm® Socius Ingredients USA
Nanocochleates	50 nm		Bioral^{TM} for omega 3 fatty acid	BioDelivery Sciences International, USA
Nanoclusters		Improved functionalities	Slim shake chocolate nanoceuticals	RBC life science, USA
			Nanococoa	Royal BodyCare, USA
Nanomicelles	100	Nano-encapsulation, improved solubility, bioactivity, sensory attributes and provide stability	Limonene, carvacrol, lutein, eugenol, omega 3 fatty acids, whey proteins, essential oils, lycopene	BASF, Germany
			Novosol for nutrients, canola active oil	Sheman factory, Israel

nano-encapsulation. The nano size of encapsulated particles leads to production of optically transparent product which enhances its application food and beverage. The literature available regarding nano-encapsulation of functional bioactive ingredients is discussed below.

21.4.1 Nano-encapsulation of Essential Oils

Essential oils (Eos) are volatile aromatic liquid obtained from plant sources. These are exploited in cosmetics industry; however, due to their antimicrobial and anti-inflammatory properties, they have potential to be used in food industry as antimicrobial compounds (Bueno-Silva et al. 2013). However, their incorporation in functional food is limited due to their peculiar aroma and flavour and their sensitivity towards light, oxygen, and heat, which can cause their degradation. Further, their poor water solubility and high volatility pose challenges to incorporate these EOs in food system (Shah 2011). Different researchers have used nano-encapsulation of EOs to protect their interaction with food components, to retain their biological activity, and to minimize their possible adverse effect on sensory properties of food. The another benefit of nano-encapsulation of EOs is enhancement in their antimicrobial properties as reducing the size to nanoscale increases the surface area for contacting bacteria (McClements et al. 2007; Weiss et al. 2009).

Woranuch and Yoksan (2013) encapsulated eugenol in chitosan nanoparticles and evaluated its thermal stability and reported eightfold higher retention and 2.7-fold higher antioxidant activity of nano-encapsulated eugenol compared to its free form during its extrusion and storage in thermoplastic flour. Flores et al. (2013) prepared nanocapsules of tea tree oil and evaluated its antifungal property against *T. rubrum* in onychomycosis model. They reported that nano-encapsulation has enhanced antifungal activity as well as provided higher protection against volatilization. Ghosh et al. (2013) determined antibacterial activity of basil oil nano-emulsions against *E. coli* and reported that 1000 times diluted nano-emulsion was sufficient enough to kill 40% of *E. coli* after 60 min of incubation, and on lowering the dilution to 10–100-fold, *E. coli* was completely inactivated after 45 min of incubation. Baldissera et al. (2013) compared antimicrobial activity of essential oils of andiroba (*Carapa guaianensis*) and aroeira (*Schinus molle*) against *Trypanosoma evansi* in their nano-encapsulated form and unencapsulated form under in vitro condition. They reported that nano-emulsion form is equally active against *T. evansi* compared to conventional form and can be used as an alternative for treatment. Balcão et al. (2013) investigated nano-emulsions of lactoferrin for its antimicrobial activity against pathogenic bacteria *S. aureus, L. innocua,* and *Candida albicans* and reported that antibacterial activity of control and encapsulated lactoferrin is similar that can be exploited in formulation of oral supplements and beverages. Jo et al. (2014) prepared nano-emulsions of lemongrass oil using carnauba-shellac wax and applied it on apple and plums as coating material. They reported that nano-emulsion loaded with lemon grass was effective against *S. typhimurium, E. coli* and yeast and mould and therefore can be used to preserve quality of fruits. Lv et al. (2014) nano-encapsulated Jasmine oil in gelatin and gum arabic nanoparticle and evaluated its structural characteristics and flavour profile at 80 °C. They reported that these nanoparticles were stable for 7 h at 80 °C. Zhang et al. (2014b) prepared thymol loaded zein nanoparticles and reported its higher effectiveness against gram-positive bacteria than unencapsulated thymol oil for a longer duration. Cui et al. (2015) evaluated antimicrobial activity of nano-encapsulated clove oil against *E. coli* and *S. aureus* and reported that encapsulated clove oil has antimicrobial activity against *S. aureus* that secrete pore-forming toxins (PFT) but did not have antimicrobial activity against *E. coli*, which does not secrete PFTs. Therefore, the secretion of PFTs causes release of clove oil from nanocapsules. Sebaaly et al. (2015) prepared clove oil nanoparticles using soybean phospholipid-based liposomes and checked its stability for 2 months at 4 °C. They reported that clove oil was protected from degradation as well as maintained antioxidant activity during storage. Eucalyptus essential was encapsulated in cashew gum nanoparticles, and their antimicrobial activity was evaluated against *Listeria monocytogenes* and *Salmonella enteritidis*. They reported that nano-encapsulated oil has more antibacterial activity against *Listeria monocytogenes* compared to *S. enteritidis* and has a potential to be used as food preservative (Herculano et al. 2015). Salvia-Trujillo et al. (2015) prepared lemongrass, clove, tea tree, thyme, geranium, marjoram, palmarosa, rosewood, sage, and mint nano-emulsion. With high-speed homogenizer, coarse emulsion was obtained which were again subjected to followed by microfluidization for nano-sized emulsion. The nano-emulsions showed better inactivation of *E. coli* in comparison with coarse emulsion that can be used as preservative in foods. Moghimi et al. (2016) prepared nano-emulsion *of Thymus daenensis* using ultrasonication and reported the enhanced antibacterial activity of nano-emulsion in comparison with free oil against *E. coli*. Sharma et al. (2017) prepared clove oil nano-emulsions by high-speed homogenizer using sodium caseinate and pectin as coating material for its delivery in food preservation as natural preservative. Sonu et al. (2018) investigated D-limonene oil (LO) nano-emulsion prepared by ultrasonication method using whey protein (WP)–maltodextrin (MD) conjugates as coating material and reported that antibacterial activity of both LO nano-emulsion and bulk LO were same against *Bacillus cereus, Escherichia coli, Enterococcus faecalis,* and *Salmonella typhi*. Therefore, LO nano-emulsion can be used as safer alternative for preservation of foods.

21.4.2 Nano-encapsulation of Vitamins

Vitamins are essentially required for the growth and the development of human body and need to be supplied through diet (Wildman 2002). Vitamins are very sensitive biomolecules and need to be protected during processing and storage for their bioactivity, and encapsulation may serve the purpose (Sanguansri and Augustin 2006). However, recent literature has suggested that nano-encapsulation is more promising in delivering and preserving bioactivity of vitamins compared to micro-encapsulation (Danino et al. 2014; Fathima et al. 2016; Gutiérrez et al. 2013).

21.4.2.1 Nano-encapsulation of Water-Soluble Vitamins

Madhaiyan et al. (2013) prepared nanofibers loaded with vitamin B12 using electrospinning technique and described increased constant release of vitamin. Zhou et al. (2014) prepared vitamin C liposome using pectin (high methoxy and low methoxy) and reported a 1.7-fold and 2.1-fold more penetration of vitamin C in high methoxy pectin liposome of vitamin C and low methoxy pectin liposome of vitamin C, respectively. Azevedo et al. (2014) prepared nano-encapsulated vitamin B2 using alginate and chitosan as wall material with higher stability compared to unencapsulated one. Jiménez-Fernández et al. (2014) prepared chitosan-based nanoparticles of vitamin C and observed a significant increase in antioxidant activity of cell during in vitro study of zebrafish liver cell line. Bou et al. (2014); Esfanjani et al. (2015); and Mohammadi et al. (2016) used double emulsions W1/O/W2 for nano-encapsulation of riboflavin using different oils (chia, sunflower, and olive oil) and found that all oils were able to encapsulate riboflavin, but the chia oil was most effective. Pérez-Masiá et al. (2015) prepared nano-encapsulated folic acid by electrospraying method using whey protein concentrate and resistant starch as wall material. Due to interaction of folic acid with protein matrix, there was increased bioavailability and stability of folic acid. Penalva et al. (2015) used casein for nano-encapsulation of folic acid and reported 50–52% higher bioavailability by using in vitro model. Assadpour et al. (2016) prepared nano-emulsions of folic acid (3 mg/ml) using maltodextrin–whey protein by spontaneous emulsification method, which is a low-energy technique.

21.4.2.2 Nano-encapsulation of Fat-Soluble Vitamins

Saberi et al. (2013) prepared nano-emulsions of vitamin E by spontaneous emulsification using medium-chain triglyceride oil and reported that the nano-emulsion was stable at room temperature but showed turbidity on heating to 53 °C. Abbasi et al. (2014) prepared nano-encapsulated vitamin D_3 using whey protein isolates with higher stability during storage in the presence of air after 7 days. Dasgupta et al. (2016) formulated nano-emulsions of vitamin E acetate using mustard oil and Tween 80 as surfactant by low-energy technique with an encapsulation efficiency of 99.65%. Bochicchio et al. (2016) prepared nanoliposomes of vitamin E and D_2 with encapsulation efficiency 72–95% by multilamellar large vesicles and 56–76% by small unilamellar vesicles. David and Livney (2016) nano-encapsulated vitamin D_3 within potato protein nanoparticle using nanoprecipitation method for its use in model beverage solution and reported decrease in vitamin loss during pasteurization. Lee et al. (2016) exposed soy protein isolate-coated vitamin D_3 nanoparticles to UV rays and reported a retention of 73.5% vitamin D_3 compared to 5.2% in unencapsulated vitamin D_3.

21.4.3 Encapsulation of Flavour and Aroma Compounds

Flavour is directly related to the quality of food and plays an important role in its consumer acceptability. Flavours are volatile components that may degrade or loss during processing and storage. Nano-encapsulation enhances stability of flavour and aroma compounds so that they can be added in foods and beverages. Because of nano size, they are better dispersible in water (Chaudhry et al. 2008). Soottitantawat et al. (2005) prepared nano-emulsion of menthol using gum arabic and maltodextrin. Baranauskienė et al. (2006) prepared nano-emulsions of natural flavour components of oregano, citronella, and marjoram using skimmed milk powder, and whey protein. Nano-encapsulation of vanillin using electrospun polyvinyl alcohol (PVA) nanofibres was prepared and reported to have higher thermal stability and prolonged shelf life (Kayaci and Uyar 2012). Liu et al. (2013) prepared nanocapsules of Naringin dihydrochalcone, which is an intense sweetener for its applications in many food and pharmaceutical products. Sosa et al. (2014) prepared encapsulated orange essential oil within modified starch/maltodextrin polymer blends, with addition of disaccharides (sucrose or trehalose). Zahi et al. (2014) prepared organogel-based nano-emulsions of D-limonene. Zhu et al. (2014) nano-encapsulated sweet orange flavour in β-cyclodextrin using inclusion complexation.

21.4.4 Nano-encapsulation of Polyphenols

Polyphenols are secondary plant metabolites and have a great potential to be used in functional food, nutraceutical, and pharmaceutical products (Scalbert et al. 2005), because of their antioxidant, anti-inflammatory, antibacterial, and antiviral activity (Bennick 2002). However, on oral intake of polyphenols, only a small portion is bioavailable because of their low permeability, solubility, and instability due to pH and enzymes in gastrointestinal tract (Bell 2001). On the other side, the polyphenols have astringent taste that needs to be masked before their addition into food. Polyphenol are majorly phenolic acids (gallic acid, hydroxyl benzoic acid, vanillic acid, caffeic acid, ferulic acid, coumaric acid, etc.) and flavonoids (flavonols, flavones, isoflavones, anthocyanidins, etc.).

Chen et al. (2014) and Sechi et al. (2016) prepared nano-encapsulated fisetin, a colouring polyphenol in fruits and vegetables, and reported that its antioxidant activity is preserved by encapsulation process. Zhu et al. (2014) described increase in vitro stability of nano-encapsulated epigallocatechin. Li and Gu (2014) studied nano-encapsulated epigallocatechin using Caco-2 cell model and presented its higher absorption compared to its free form. According to Wei et al. (2014), baicalin liposomes have threefold higher bioavailability and higher concentration of baicalin in liver, kidney, and lungs because of pharmacokinetics and biodistribution studies in rats. Zhang et al. (2014a) also studied nano-encapsulated baicalin than its free form on HepG2 cell and reported lower IC50 value. Liu et al. (2014), and Chen et al. (2015) also described higher bio-accessibility of nano-encapsulated luteolin and nobiletin, respectively. Sun et al. (2014) found that nanostructured lipid carrier for quercetin has higher solubility and stability. Ban et al. (2015) prepared lipid nanoparticles of hesperetin and naringenin with higher bio-accessibility of >71%. Ting et al. (2015) reported higher efficiency of tangeretin nano-emulsions in inhibiting colon cancer by using in vivo and in vitro models. Gonçalves et al. (2015) measured antioxidant activity of quercetin nanosuspensions that showed higher antioxidant activity compared to its free form. Sanna et al. (2015) presented higher retained antioxidant activity of catechin extract from tea after nano-encapsulation. Sharma et al. (2015) reported higher antioxidant activity of rutin nano-emulsions compared to pure rutin. Arroyo-Maya and McClements (2015) and Ravanfar et al. (2016) described higher stability of nano-encapsulated anthocyanin at high pH and temperature. Nallamuthu et al. (2015) evaluated chitosan-based chlorogenic nanoparticles and reported a controlled release profile as 25% fast release in 10 h and then 69% slow release until 100 h. These nanoparticles were found to be thermally stable. According to Fernández et al. (2016), proanthocyanidins from nano-encapsulated grape seed had sustained release during in vitro release study. Ni et al. (2017) prepared nano-emulsions of quercetin, and it showed higher bioavailability. Wang et al. (2016) found higher antitumor activity of freeze-dried nanoparticles of quercetin using in vivo model. Kumar et al. (2016) described higher antimicrobial activity of quercetin nanoparticles than its free form. According to Tripathi et al. (2016), nano-emulsion of genistein has 2.8-fold higher bioavailability in pharmacokinetics study. Alves et al. (2016) described higher stability and enhanced release during in vitro analysis of nano-encapsulated gallic acid. Nourbakhsh et al. (2017) prepared bioactive peptide-based nanoparticles of gallic acid for preparation of value-added products. Katuwavila et al. (2016) investigated nano-encapsulated caffeic acid for its antioxidant activity and reported no reduction after encapsulation as well as slow release up to 7 h.

21.4.5 Nano-encapsulation of Carotenoids

Carotenoids (beta carotene, lycopene, lutein, astaxanthin, canthaxanthin, etc.) are mainly used as natural food colourant as well as antioxidant in food. However, their addition into food formulation is difficult because of their low solubility in water as well as oil and susceptibility to oxygen, light, and heat that makes them unstable in food (Xianquan et al. 2005). Nano-encapsulation can enhance their solubility and prevent deterioration during processing. Pan et al. (2007) reported amphiphilic nature of nano-encapsulated beta carotene using casein and dextran. Wang et al. (2008) prepared curcumin oil-in-water nano-emulsion using high-pressure homogenization and observed enhanced anti-inflammatory action of curcumin in mouse ear inflammation model. Yu and Huang (2010) prepared nanocapsules of curcumin and reported increase in vitro anticancer activity of encapsulated curcumin as compared to free curcumin. Ahmed et al. (2012) prepared curcumin nano-emulsion using short-chain triglycerides, medium-chain triglycerides, and long-chain triglycerides, and greater bio-accessibility was observed for medium-chain triglycerides as compared to short-chain and long-chain triglycerides.

Qian et al. (2012) used beta lactoglobulin for nano-encapsulation of beta carotene and reported slower degradation of encapsulated beta carotene at higher temperature. Wang et al. (2013) reported higher stability of nanocapsulated xanthophyll coated with polyvinyl pyrrolidone and sodium alginate using ultrasonication. Gutiérrez et al. (2013) prepared reassembled nanomicelle using casein and reported to be protected against thermal degradation and oxidation. Sáiz-Abajo et al. (2013) reported 70% retained beta carotene in sodium caseinate encapsulated beta carotene after 8 h of heating at 80 °C. Ravi and Baskaran (2015) prepared fucoxanthin nanogels using chitosan and glycolipid. Silalai et al. (2016) nano-encapsulated mangostin using whey protein, maltodextrin, and combination thereof and resulted in increased stability. Coronel-Aguilera and San Martín-González (2015) prepared nanocapsules of beta carotene using cellulose by fluidized bed drying at 70 °C. Sari et al. (2015) prepared curcumin nano-emulsion using medium-chain triglyceride by ultrasonication and reported that curcumin nano-emulsion was relatively resistant to pepsin digestion but pancreatin causes release of curcumin from nano-emulsion in in vitro simulated gastrointestinal studies.

21.4.6 Nano-encapsulation of Essential Fatty Acids

Poly unsaturated fatty acids (PUFAs) like, linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) have a role in lowering blood serum triacylglycerol and cholesterol concentration (Harris et al. 2008), proper development and function of the brain and retina immune-modulating properties as well as role in prevention of cardiovascular diseases, decrease in the risk of some types of cancer and autoimmune disorders (Kschonsek et al. 2016; Song et al. 2016). However, the rich sources of PUFAs like fish oils and flaxseed oils are oxidized very easily during processing and storage of food as well as provide strong odours in the final product. Therefore, researchers have used nano-encapsulation of these ingredients for their incorporation in functional foods. Zimet and Livney (2009) prepared nanocapsules of omega 3 fatty acids using β-lactoglobulin and pectin and reported that nano-encapsulation provided protection against oxidation during an accelerated shelf-life test. Borneo et al. (2007) prepared cream-filled sandwich cookies added with encapsulated omega-3 fatty acids and reported no adverse effect on sensory and shelf stability of cookies. Gökmen et al. (2011) investigated bread added with nano-encapsulated flaxseed oil and reported significant reduction in lipid oxidation, acrylamide, and hydroxyl methyl furfural in bread. Ghorbanzade et al. (2017) prepared nanoliposomes of fish oil and fortified into yogurt and reported a higher DHA and EPA contents in yogurt than yogurt containing free fish oil. Abbas et al. (2013); Berton-Carabin et al. (2014), Esquerdo et al. (2015), Fernandez-Avila and Trujillo (2016), Hebishy et al. (2015), McClements and Gumus (2016), and Santiago and Castro (2016) used nano-emulsification by high-pressure homogenization approach for preparation of nano-emulsion of poly unsaturated fatty acids for protection against oxidation. Ilyasoglu and El (2014) prepared nano-encapsulated EPA and DHA using sodium caseinate and gum arabic for their incorporation in fruit juice.

21.4.7 Nano-encapsulation of Minerals

Minerals are micronutrients which are required in small quantity in the body. Direct fortification of food with minerals has a substantial influence on the mineral bioavailability. Nano-encapsulation of mineral will be a promising technology for their fortification in food due to the inhibition of interaction with other components, masking of off flavour and colour as well as controlled release of mineral components. The detail review (Gharibzahedi and Jafari 2017) has highlighted the mineral fortification with nano-encapsulated minerals with especially Fe, Ca, Zn, and I. Fe-encapsulated forms used as core materials in fortifying dairy products are electrolytic-Fe, $FeSO_4$, $FeSO_4 \cdot 7H_2O$, $C_4H_8FeN_2O_4$, $NH_4Fe(SO_4)_2$, and $C_6H_{10}FeO_6$. Encapsulated forms of two Ca salts of tricalcium phosphate ($Ca_3(PO_4)_2$) and calcium citrate ($Ca_3(C_6H_5O_7)_2$) have also been applied to fortify soy-yogurt and soymilk. The most popular encapsulated formulas of iodine and Fe for fortifying edible salts are KI and KIO_3, and $C_4H_2FeO_4$ and $FeSO_4$, respectively. Nevertheless, some attempts have been made to develop fortified bakery products based on flours nano-encapsulated with minerals as suitable vehicles (Gharibzahedi and Jafari 2017).

21.4.8 Nano-encapsulation of Probiotics

Probiotics are live bacterial cells which have a beneficial effect on human gut microflora. These are incorporated in fermented foods like yoghurts, cheese, puddings, and fruit-based drinks. Food incorporated with encapsulated probiotic bacterial will have longer shelf life of the product, and nano-encapsulated probiotic bacteria can be designed to release at certain parts of the gastrointestinal tract where they interact with specific receptors (Vidhyalakshmi et al. 2009). Ebrahimnejad et al. (2017) prepared chitosan-based nanocapsules of *Lactobacillus acidophilus* and reported increased viability and survival against gastrointestinal environmental conditions. Kalal et al. 2017 nano-encapsulated *Lactobacillus casei* in bitter gourd juice using maltodextrin by spray drying and reported viability of counts for 4 weeks. Noori et al. (2017) prepared nanoliposomes *Lactobacillus casei* and *Bifidobacterium lactis* and reported increased stability of natural compounds, during different processes.

21.5 Characterization of Nanoparticles Encapsulating Bioactives

Nanoparticles are reactive and their properties like size, shape, solubility, chemical composition etc. changes with change in environmental conditions (Rogers et al. 2007). Physical and chemical properties of nanoparticles are also important to be determined with their composition and concentration, as it will influence behaviour of nanoparticles. There are several techniques available for detection and characterization of nanoparticles. Following are the properties of nanoparticles that need to be analysed for its potential toxicity and behaviour (Borm et al. 2006; Chau et al. 2007):

1. Size and size distribution that describe its transport behaviour and bioavailability;
2. Surface charge that determines stability of nanoparticles especially in dispersions;
3. Shape (spherical/tubular) of nanoparticle which affects its transport through membranes in cell as well as antimicrobial behaviour;
4. Elemental composition that leads to different particle behaviour and its impact on toxicity.

Analytical methods are applied for characterization of nanoparticles to identify whether a certain substance is present in the sample and to quantify how much of the substance is in the sample (mass or number of particles) (Koeber et al. 2010). In general, the characterization of nanoparticles is based on size (mean particle size) and homogeneity of size distribution poly-dispersity index (PDI). The mean particle size is the most basic information and measured in terms of diameters of nanospheres. The PDI reflects the size distribution of nanoparticles. The higher PDI value means sample contains wide range of particle size, while lower PDI values indicate evenly sized particles in sample. Most of the available techniques are for mass-based PDI distribution, and there are no reliable methods available for the determination of accurate number-based size distributions. Different techniques are used for characterization of nanoparticles and can be divided into two broad categories:

(i) Physical techniques—These techniques are used to know the size and shape of the nano-encapsulated particles
(ii) Analytical chemistry techniques—These techniques are used to identify or for confirmation of the nano-encapsulated material

21.5.1 Physical Techniques

Dynamic light scattering (DLS): Dynamic light scattering (DLS) measures the hydrodynamic diameter of particles. DLS measures Brownian motion of nanoparticles in suspension and average diameters since light scattering capacity of particles, which gives greater weightage to larger particles. The result is reported as a mean particle size and homogeneity of size distribution PDI. A PDI value from 0.1 to 0.25 indicates a narrow size distribution, and a PDI value greater than 0.5 indicates a broad distribution. Sonu et al. (2018) studied limonene oil nano-emulsions stabilized by whey protein–maltodextrin conjugate. Sari et al. (2015); Sharma et al. (2017) characterized clove oil nano-emulsion and curcumin nano-emulsions using DLS. Different other workers (Bootz et al. 2004; Brant et al. 2005; Lecoanet et al. 2004; Lecoanet and Wiesner 2004; Phenrat et al. 2007) also utilized DLS for characterization of nanoparticles. DLS is a rapid and simple analytical tool that provides an estimate of the particle size; however, it is relatively poor at analysing multimodal particle size distribution and provides only data of one-dimensional scattering (Luykx et al. 2008). In DLS, the aggregates are difficult to quantify; therefore, size cannot be correlated with specific composition (Bootz et al. 2004).

Microscopy: It is an imaging technique for measuring size, shape, and aggregation state of nanoparticles. Transmission electron microscope (TEM), scanning electron microscope (SEM), and atomic force microscopy (AFM) are most popularly used for visualization of nanoparticles. In TEM, electrons are passed through sample specimen (very thin 1 μm) and output appears on fluorescent screen or a photographic film or detected by a sensor. Different researchers have used TEM to characterize nanoparticles. Graveland-Bikker and De Kruif (2006) studied milk protein-based nanoparticles. Vogel et al. (2002) studied serum albumin-based nanoparticles. It has also been applied to investigate the surface properties of nanoliposomes (Jores et al. 2004; Kosaraju et al. 2006; Mozafari et al. 2007). However, it requires an extensive sample preparation to have a very thin sample specimen; therefore, it is a time-consuming technique with low throughput of samples (Wang 2000). Kong and Park (2011); Singh et al. (2013) also utilized TEM for characterization of food nanoparticles.

SEM produces high-resolution images of 3D appearance and can be used to describe surface morphology of sample (Goldstein et al. 2017). Due to large depth of field, it can focus on large amount of sample at a time. Bertholon et al. (2006) used it for characterization of polysaccharide nanoparticles, and Parris et al. (2005)

studied surface morphology of zein encapsulated essential oil. Taylor et al. (2005) studied SEM for release of content through liposomes. However, it is also an expensive technique and requires a high vacuum with high conductivity of sample (Fraunhofer and Winter 2004). Khurana et al. (2013) compared results of DLS with TEM and reported the bigger size in TEM analysis than the hydrodynamic size.

Sharma et al. (2017) utilized both SEM and TEM techniques for characterization of clove oil nano-emulsions. Scanning electron micrographs showed spherical nanoparticles, whereas transmission electron micrographs confirmed the morphology through discrete spherical droplets with defined boundaries of core and coating material.

AFM has an advantage of imaging any type of surface which may or may not be conducting or semiconducting surface and analysis can be carried out in fully liquid conditions. It provides an accurate assessment of the size and shape of nanoparticles; however, it requires complicated sample preparation steps specific to microscope techniques which can change samples properties. Moreover, it is difficult to obtain particle size distribution. Many studies (Liang et al. 2004; Moraru et al. 2003; Palmer et al. 2003; Yegin and Lamprecht 2006) used AFM for characterization of liposomes and lipid nanocapsules. Lead et al. (2005) and Wigginton et al. (2007) also used AFM for characterization of aquatic nanoparticles. Yang et al. (2007) described different application of AFM in characterization of nanoparticles in food science.

Nanoparticle Tracking Analysis (NTA): This is imaging method, based on dark field or fluorescence microscopy in which size is derived with its correlation with the Brownian motion. It does not provide the information related to chemical composition, but provides a high resolution for multimodal samples and observable aggregation phenomenon. However, to avoid overly crowed observation fields, it requires a sample to be sufficiently diluted. Luo et al. (2013) characterized nanoparticles in tomato soup, and Gallego-Urrea et al. (2011) studied gold nanoparticles in orange juice using NTA.

21.5.2 Analytical Chemistry Techniques

Mass Spectrometry: This technique can be used to confirm the identity of encapsulated material. It consists of ion source and mass analyser; detector can identify unknown compounds and their concentration. Different types of mass spectrometry are applied for characterization of nanoparticles (MALDI, ESI, and ICP-MS). MALDI mass spectrometry is applied for fluorescent nanoparticles (Cai et al. 2003; Peng et al. 2003). It was used by Zhang et al. (2006) for characterization of chitosan-derived nanoparticles and by Lee et al. (2005) for PEG conjugated nanoparticles. Carstens et al. (2006) and Carstens et al. (2007) used ESI for characterization of PEG-oligolactates and PEG-oligocaprolactones. Bolea et al. (2006) used ICP-MS for distribution of colloidal material and adsorption of trace metal on colloids.

NMR Spectroscopy: It is non-destructive method related to the absorption of radiofrequency by atom in a strong magnetic field (Ibañez and Cifuentes 2001). Li et al. (1994) and Sun and Wan (2007) utilized NMR as a tool for characterization of nanoparticles.

X-Ray Diffraction: This technique is a non-destructive that can identify crystalline solids on their atomic structure. Some researchers (Attama et al. 2006; Barauskas et al. 2005; Lalush et al. 2005) utilized X-ray diffraction for characterization of lipid-based nanoparticles, and some (Kavanagh et al. 2000; Lochmann et al. 2005; Yuan et al. 2007) used for characterization of protein-based nanoparticles.

Laser Doppler Electrophoresis: Surface charge is an important property related to nanoparticles and is expressed as zeta potential. Laser Doppler electrophoresis evaluates electrophoretic mobility for measuring zeta potential. Zeta potential is related to stability of particle in a medium and represents the overall charge on particle. Particles having large negative (−30 mV) and positive (+30 mV) charge leads to higher stability due to electrostatic repulsion. It is necessary to mention the pH of solution while reporting zeta potential as its measurement depends on the strength and valency of ions in the nanoparticle suspension. Some studies reported zeta potential of limonene oil nano-emulsions, clove oil nano-emulsion, and curcumin nano-emulsions using zetasizer (Sari et al. 2015; Sharma et al. 2017; Sonu et al. 2018).

21.6 Challenges Associated with the Nano-encapsulation of Bioactive Ingredient

Selection of wall material and the method of preparation of nanoparticles encapsulating bioactive ingredient are of utmost importance as well as challenging. Although the prepared nano-encapsulated bioactive ingredient may be stable in their pure form under controlled environment; however, when they are incorporated into food, their stability becomes major concern. During processing and storage, the delivery system should protect bioactive compounds from degradation due to temperature, light, pH, during food manufacturing, storage, and preparation (McClements et al. 2007). Under these conditions, if there is collapse of structural material, it can adversely impact the stability of encapsulated bioactive ingredient. Another challenges for preparation of nanoparticles to be incorporated in food is the replacement of polymers and surfactants with food grade alternatives (Acosta 2009) and design of stable delivery system that has minimal impact on the organoleptic properties of the product (Donsì et al. 2011). Besides this, during preparation of nanoparticles, the release mechanisms of bioactive ingredients during their passage from entire GIT and controlled release at targeted sites should be considered because delivery system should maximize the uptake (Acosta 2009). Finally, another important criterion is prepared nanoparticles and its process of preparation must be technically and economically feasible as well as up-scalable from the laboratory to pilot scale (Donsì et al. 2010a, b).

The characterization of nanoparticle is a challenging task as it does not mean size of nanoparticles but also to provide particle size distribution based on number rather than the mass because when there is a decrease in particle diameter, the particle number concentration increases and definition of nanoparticle by European commission also relates to number weighted particle size distribution. However, the size of a nanoparticle is method-defined property because non-spherical particle can be characterized in multiple sizes depending upon the method used. Available techniques will provide uniform characterization only if they are perfect spherical as well as not aggregated or complexed with any other material. Different analytical methods have different limits of detection in terms of size and concentration, and without prior knowledge of instrument results, the interpretation of size will lead to inaccurate or biased output. For accurate values of detection limit (in terms of nanoparticle size), reference material with wide range of number-based particle size distribution is required. All available certified reference materials (CRMs) are based on weight-based particle size distribution, and so far, no CRM is available that is certified based on particle number. This poses a challenge in accuracy and validation of nanoparticles. Depending upon the technique, sample preparation/ digestion is required, and there are chances that nanoparticles may undergo physical and/or chemical changes; therefore, the results obtained can differ from in situ behaviour of nanoparticle (Burleson et al. 2004). Nanoparticle analysis is a four-dimensional analysis that includes spatial resolution (for small objects), energy or spectroscopy (for composition and chemical analysis), time (considering the dynamic and time variation of these materials), and environment. Nanoparticles are highly reactive materials because of high surface and interface areas of that leads to environmentally induced changes. The handling of sample, processing, storage time, and exposure to temperature and pressure may affect the state of nanoparticles. As change in pH and ionic strength may cause agglomeration of nanoparticles and dilution may also influence suspended solid content, dissolved substance, nanoparticle processing for characterization may lead to chemical modification and sometimes losses of nanoparticles may also occur due to sorption to walls and filters. A lot of work has been reported regarding sample preparation for analysis of nanoparticle, especially microscopic examination (Bootz et al. 2004; Paunov et al. 2007). Nanoparticles are not unique stable entities, and due to their nano size, a small amount of energy may readily change their shape or structure. Different analytical techniques involve a significantly larger energy than those associated with nanoparticles, and they may have significant impact on what is measured. Analysis of nanoparticles incorporated in food is much more complex than their analysis in pure form, because for their detection and characterization in food, they need to be extracted from food matrix with minimum manipulation for analytical accuracy. The time and storage conditions between the sample preparation and analysis are also very crucial, as it may cause destabilization of nanoparticles (agglomeration, dissolution, etc.) and leads to error in analysis. This may also affect reproducibility of results, the up-scaling of process and their risk assessment.

Concern has been shown towards the use of nanoparticle in food applications due to toxicity associated with them. Toxicity of nanoparticles is associated with their size and their ability to cross biological barriers. A healthy digestive system only allows absorption of nutrients from the gut after digestion of ingredient, but due to small size of nanoparticles, there are chances that without degradation (partial or fully) they get absorbed through intestine and can pose risk to human. It is reported that on ingestion of nanoparticles encapsulating bioactive ingredient pro-oxidants are formed and it can disrupt the balance between the production and detoxification of reactive oxygen species that can cause oxidative damage to cell. For absorption of nanoparticles, they need to overcome enzymes, acidic pH, mucus membrane, and selective permeability of intestinal cell (Chen et al. 2011; Ensign et al. 2012). Size, charge, and hydrophobicity of nanoparticles play a very important role in their absorption, distribution, metabolism, and excretion. Less than 100 nm size nanoparticles are highly absorbed (Lai et al. 2007), 100–200 nm are moderately absorbed (Acosta 2009), low absorption of 300–500 nm and no absorption of particles with size more than 500 nm (Norris et al. 1998) through mucus membrane of intestine. Less than 50 nm are highly absorbed (Faraji and Wipf 2009; Florence 2005), 100–400 nm is moderately absorbed (des Rieux et al. 2006) and low absorption of more than 500 nm (Sahay et al. 2010) through enterocytes/M cells of intestine. Positively charged nanoparticles adhered to mucous, and there is low absorption of negatively charged nanoparticles compared to uncharged nanoparticles in mucus (Lai et al. 2009). Through enterocytes/M cells positively charged nanoparticles are highly absorbed compared to negatively charged and uncharged nanoparticles (Sahay et al. 2010) and promote an immune response (Naahidi et al. 2013).

Acosta (2009) reported that hydrophobic nanoparticles are highly absorbed compared to hydrophilic nanoparticles through enterocytes/M cells; however, no such consensus was reported for absorption through mucus membrane (Hussain et al. 2001; Lai et al. 2009; Powell et al. 2010). Hydrophobic nanoparticles are more likely to recognize as a foreign object in blood compared to hydrophilic nanoparticles (Naahidi et al. 2013).

After absorption, nanoparticles can be taken up by gut-associated lymphoid tissue or by liver and further they reach into systemic circulation (Chen et al. 2011) and then they are transported to various organs such as the heart, lungs, spleen, kidney, liver, and brain (Aillon et al. 2009). The release of bioactive ingredient may be either in intestine, systemic circulation or at the organ tissues (Chen et al. 2011), and their release depends upon the type of delivery nanoparticles and their sensitivity to pH and enzymes (Quintanilla-Carvajal et al. 2010). The uptake of bioactive will depend upon chemical, morphological, and physical properties in intestine, its interaction with blood components in systemic circulation, and cellular interactions at organ tissue. Depending upon their solubility (water-soluble or fat-soluble), they may follow different pathways (Sahay et al. 2010).

21.7 Conclusion

Nanotechnology is an emerging field of science. Many applications of nanotechnology in preparation of functional food systems as well as processing have been developed in many countries, such as nano-sized-based delivery systems for functional components, active and intelligent packaging system, etc. Nanotechnology has a great potential in food processing industries to improve the nutritional and sensory profile by generating nanofoods, packaging system as well as techniques. However, the application of nanotechnology in the food sector is still in the initial stage, as there is always a risk associated with nano size because the physiochemical properties of particles in nano and macro sizes are different, and as the size decreases, there are more chances of crossing cell barrier and reach to organ in body. The bio-accumulation of nanoparticles within body organs like liver, kidney and spleen and other tissues may increase the deleterious effect (Savolainen et al. 2010). Limited literature is available regarding safety assessment of nano-encapsulated bioactive ingredient in the presence of other food component. In August 2006, the FDA has formed Nanotechnology Task Force to regulate continued development of products based on nanotechnology materials. However, up to now, there has been no conclusive report regarding undesirable effect of nanotechnology in food system or health (Chau et al. 2007). Food and Agricultural Organization (FAO) and World Health Organization (WHO) have prepared a technical paper regarding risk associated with nanotechnology in food and agriculture sector. Several food products based on nano-encapsulation are entering into the market; therefore, there is a need for regulating these types of products at international level. FAO and WHO identified the status of different regulatory authorities working in different countries regarding regulation of nano-based foods (Takeuchi et al. 2014). The safe application of nanoparticles in food and agricultural requires knowledge of their ADME (absorption, distribution, metabolism, and excretion) and toxicological profiles. With more scientific inputs, the commercialization of nano-based food can be solved. However, improving public acceptance, economics and realistic regulation are also important for the successful future application of nanotechnology in the functional food industry.

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Chapter 22
Nanomaterials for Active and Smart Packaging of Food

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Abstract Need for the storage and transport of food materials into different geographical locations stimulated the requirement of various advances in packaging. Active and smart packaging add new dimension in the packaging industry by contributing various performance characteristics in addition to storage and transportation. The requirements of online monitoring, monitoring and control of pest and diseases, controlled ripening of fruits, sensing the spoilage of food materials, etc., could be satisfied by the innovative packaging like active and smart packaging. For better and efficient performance, the nanomaterials come handy due to their size and efficiency. This chapter focuses on the use of various nanomaterials in active and smart packaging.

Keywords Active packaging · Intelligent packaging · Silver · Smart packaging · Zinc oxide · Biosensor

22.1 Introduction

Packaging is defined as enclosure of product to protect it from tampering or contamination from physical, chemical, and biological sources. Packaging maintains the benefits of food processing after the process is complete, ensuring the safety, wholesomeness, and quality of food when it reaches to consumer (Prasad and Kochhar 2014). The primary functions of food packaging are containment, protection, convenience, and communication (Yildirim et al. 2018). Food package must contain or store the product to function successfully. The containment function ensures prevention from product loss and pollution. Protection is often regarded as the most important primary function of the food package. Packaging has been designed to protect the food against attack from microbial and chemical contamination, oxygen, water vapor, off-flavors, ultraviolet light, dust, shocks, and

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vibrations and protect the environment from the product. The type of packaging used therefore has an important role in determining the shelf life of food. Packaging plays a vital role in meeting the demands of the consumer for convenience. The food package must be easy to handle and convenient to use. For example, sauces, dressings, condiment packages can be applied easily through aerosol or pump-action which help to minimize mess as well as loss. The food package must protect what it sells and must sell what it protects. It should function as silent salesman providing information about the properties of the enclosed product (Mane 2016). In addition, food packaging should have good machinability, ensuring good performance in production line for filling, closing collating without much stoppages. This chapter reviews the current progress in research and development of active and intelligent packaging for the satisfaction of consumer demands for improved quality and prolonged shelf life for packaged foods.

Continuous innovation in food-packaging industry for more advanced and creative packaging materials has reflected the dynamic changes in current consumer demands and market trends. With increasing concern about the food safety, the consumption of natural high-quality non-processed or minimally processed foods, no preservative foods with acceptable shelf life has heightened (Singh et al. 2011; Gerez et al. 2013). In response, the new concepts of active and intelligent packaging become popular due to their ability to maintain or prolong the shelf life while ensuring quality, safety, and integrity (Fig. 22.1) (Gontard 2006). Active packaging does more than simply providing an inert barrier to outside environment. It can control and even react to, events taking place inside the package (Kale et al. 2003). Active packaging has been originally defined by Labuza and Breene (1989) as “the packaging which is used successfully to increase the shelf life of processed foods and meet consumer demands in terms of providing high-quality products that are also fresh and safe”. Rooney (1995) and Hotchkiss (1997) described active packaging as “the incorporation of certain material into packaging for maintaining and extending product shelf life”. The term active packaging is not synonymous with intelligent or smart packaging, which refers to “the packaging which is capable of sensing and providing information about the function and properties of packaged

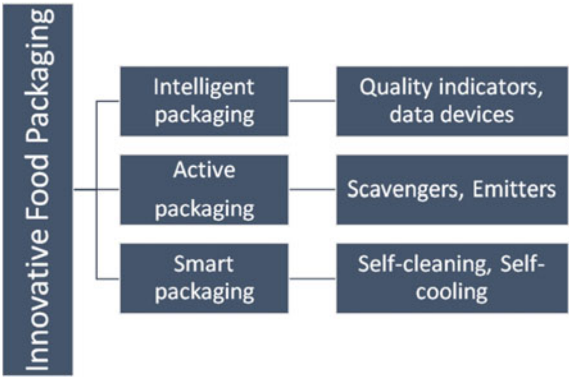

Fig. 22.1 Categorization of innovative food packaging

food". Intelligent packaging devices include time and temperature indicators, gas-sensing dyes, microbial growth indicators, and physical shock indicators (Summers 1992; Day 2001). Intelligent packaging has been defined as "packaging systems which monitor the condition of packaged foods to give information about the quality of the packaged food during transport and storage" (Ahvenainen 2008).

22.2 Types of Active Packaging

Active packaging is categorized into two different types: active scavenging systems (absorbers) and active releasing systems (emitters) (de Kruift et al. 2002). Under the scavenging packaging system, unnecessary compounds such as oxygen, moisture, and ethylene are removed from the product. Oxygen may cause off-flavors, nutrient loss through oxidation and color changes and hence the usage of oxygen scavengers to maintain quality and extend shelf life of some food products (Berenzon and Saguy 1998). The moisture content of packed horticultural products needs to be controlled as the high moisture content favors microbial growth. The softening of dry crispy food products like biscuits and caking of coffee result from the excessive moisture content. Moisture controlling systems are often used to scavenge excess moisture that contributes to product quality loss. But excess moisture loss might impose lipid peroxidation and desiccation of the packed products. Hence, a good understanding of product physiology, structure, and composition is required when designing the packaging system. Active releasing packaging system involves the addition of beneficial agents to package to preserve the quality of the content. Releasing the packaging system favors the use of compounds such as CO_2, moisture, preservatives, and antioxidants into the package. Carbon dioxide-releasing systems are also used to retard the respiration rate of horticultural crops and subsequently prolong shelf life. The main objective of active packaging, with both scavenging and releasing systems, is ensuring exceptional food quality and extended shelf life.

Other than these two categories, there are active control systems such as temperature control and microbial and quality control. Active packaging is typically found in two forms; sachets and pads which are placed inside of packages, and active ingredients that are incorporated directly into packaging materials. The different types of active packaging systems currently being used in food industry and their potential benefits are summarized below and in Table 22.1. The commercially available active packaging details are given in Table 22.2.

22.2.1 *Oxygen Scavengers*

The presence of high oxygen in the headspace of food packages may cause significant reduction in the shelf life of food by the way of oxidation of pigments and

Table 22.1 Active packaging systems and their food applications (Mane 2016)

Active scavenging systems	Mechanisms	Form	Food applications	Function
Oxygen scavengers	• Ferrous compounds • Metal/acid • Metal (e.g., platinum/ Palladium) catalyst • Ascorbate/metallic salts	Sachet, label, cap or film	Bread, cakes, cooked rice, biscuits, pizza, pasta, cheese, cured meats and fish, meat, coffee, snack foods, dried foods, and beverages	Prevention of discoloration, oxidation, mold growth, browning, rancidity, Retention of vitamin C content
Carbon dioxide scavengers	• Iron oxide/calcium hydroxide • Calcium oxide/ activated charcoal	Sachet or film	Roasted coffee, cheese, fresh meats and fish, nuts and other snack food products and sponge cakes	Extension of microbiological shelf life, adsorb produced CO_2 to prevent swelling of the package
Carbon dioxide emitters	• Ascorbate/sodium bicarbonate • Ferrous carbonate/ metal halide	–	Vegetables	Control ripening of vegetables
Ethylene scavengers	• Aluminum oxide + potassium permanganate • Cristobalite • Activated clays • Zeolites	Sachet or film	Fruit, vegetables and other horticultural products	Reduction in ripening and senescence, thereby enhancing quality and prolonging shelf life
Ethanol emitters	• Alcohol spray • Encapsulated ethanol	Sachet	Bakery products and semi-dry fish	Prevent microbial growth and staling
Moisture absorbers	• PVA blanket • Activated clays and minerals • Silica gel • Glycerol	Sachet or film	Dry foods, fish, meats, poultry, snack foods, cereals, fruit, and vegetables	Extension of shelf life through controlling moisture content, reduction in browning or discoloration

(continued)

Table 22.1 (continued)

Active scavenging systems	Mechanisms	Form	Food applications	Function
Antimicrobials	• Organic acids • Silver zeolite, zinc oxide • Spice and herb extracts • BHA/BHT antioxidants • Vitamin E antioxidant • Volatile chlorine dioxide/sulfur dioxide • Chitosan	Sachet or film	Fish, fresh and processed meat, seafood, cheese, fresh dairy products, fruit, grains, cereals, and bakery products	Inhibition or retardation of microbial growth, extension of the shelf life
Antioxidants	• BHT (butylated hydroxytoluene) • BHA (Butylated hydroxyanisole) • Vitamin C or E	Film	Fatty fish and meat, fat-containing instant powders, seeds, nuts, oils, fried products, and wine	Prevent lipid oxidation, Improvement of oxidative stability
Flavor/odor absorbers	• Cellulose triacetate • Acetylated paper • Citric acid • Ferrous salt/ ascorbate • Activated carbon/ clays/zeolites	Film	Fruit juices, fried snacks, fats & oils, fish, cereals, poultry, dairy products	Preserve smell and taste, remove off-odors

Table 22.2 Commercially available active packaging systems (Biji et al. 2015)

Trade name	Manufacturer	Principle	Type
Ageless	Mitsubishi Gas Chemical Co. Ltd., Japan	Fe based	O_2 scavenger
Freshilizer	Toppan Printing Co. Ltd., Japan	Fe based	O_2 scavenger
Freshmax, freshpax, fresh pack	Multisorb Technologies, USA	Fe based	O_2 scavenger
Oxyguard	Toyo Seikan Kaisha Ltd., Japan	Fe based	O_2 scavenger
Zero2	Food Science Australia, Australia	Photosensitive dye	O_2 scavenger
Bioka	Bioka Ltd., Finland	Enzyme based	O_2 scavenger
Dri-Loc®	Sealed Air Corporation, USA	Absorbent pad	Moisture absorber
Tenderpac®	SEALPAC, Germany	Dual compartment system	Moisture absorber
Biomaster®	Addmaster Limited, USA	Ag based	Antimicrobial
Agion®	Life Materials Technology Limited, USA	Ag based	Antimicrobial
SANICO®	Laboratories STANDA,	Antifungal coating	Inter-leavers
Neupalon	Sekisui Jushi Ltd., Japan	Activated carbon	Ethylene scavenger
Peakfresh	Peakfresh Products Ltd., Australia	Activated clay	Ethylene scavenger
Evert-fresh	Evert-Fresh Corporation, USA	Activated zeolites	Ethylene scavenger

vitamins, off-odors development, enzymatic browning, microbial growth, color change and loss of and nutritional losses (Ozdemir and Floros 2004; Cichello 2015). The control of oxygen levels in food packages is therefore of paramount to inhibit or reduce these deteriorative and spoilage reactions in foods.

Oxygen inside the headspace of packaging can be removed by vacuum sealing or by inert gas flushing (N_2, CO_2). These techniques can remove about 90–95% of the oxygen present in air from the packed food prior to or during packaging. However, the presence of residual oxygen in package may hamper the use of vacuum sealing or gas flushing techniques. Removal of this residual oxygen presents in void-space between food particles or oxygen dissolved within the food is crucial to provide extended shelf life of various foods (Mexis et al. 2012; Cichello 2015). An internal system which continually absorbs or scavenges residual oxygen inside the packaging or the oxygen that transmits through the packaging is required (Cichello 2015). A variety of oxygen absorbers or scavengers developed to control the oxygen level within the package (Brody et al. 2001; Fang et al. 2017). The oxygen absorbers or scavengers are commercially available in two forms (Poubol and Izumi 2005):

- Independent elements in the form of sachets, pouches, bags, strips, or labels, which are incorporated into or attached to the inside of the package. They are the most commonly used forms of oxygen scavengers.
- Elements integrated into the packaging material itself, not visually perceptible as distinct elements.

The type and amount of oxygen-absorbing element used in a sachet or pouches is determined by the initial oxygen level in the package, the amount of dissolved oxygen present in the food, the permeability of the packaging material, and the properties of food (size, shape, weight, fat content, water activity, etc.) (Tewari et al 2002). Oxygen scavengers in the form of sachets are not suitable for liquid foods, as the direct contact of with the sachet may cause the migration of sachet contents. In addition, sachets may cause accidental consumption with the food or may be ingested by children. Oxygen-scavenging sachets required to be labeled “Do not eat,” for safety reasons and regulatory purposes mandated by the Food and Drug Administration (FDA). The oxygen scavengers embedded in packaging film material or introduced into various layers of the packaging material, like adhesives, polish, or enamel layers. This is an efficient way to resolve sachet-related problems (Rooney 1995; Dainelli et al. 2008). Multi-layer oxygen scavengers more effectively absorb oxygen than one-layer scavenging systems. The different mechanisms of action of oxygen scavengers are discussed below. The nanoparticles used as oxygen scavenger are summarized in Table 22.3.

22.2.1.1 Oxidation of Iron and Iron Salts

This is the most effective and most widely used method of oxygen scavenging. This system consists of small sachet made up of material highly permeable to oxygen, in which iron powder is kept and oxidized to iron oxide in the presence of oxygen and water (Cichello 2015). The first oxygen-scavenging system—‘Ageless’ developed and introduced to the food-packaging market by the Mitsubishi Gas Chemical Company was based on the oxidation of iron powder by chemical means. The iron-based oxygen scavengers can scavenge oxygen in many foods, including high, intermediate, or low moisture foods, and foods containing lipids (Suman and Suk 2018). They can be effectively used as oxygen scavengers at refrigerated as well as frozen storage conditions, and suitable with microwaveable food products. The only drawback is these systems may impart undesirable flavor to the foods in contact.

22.2.1.2 Oxidation of Antioxidants

Antioxidants are generally oxidized by radicals from lipids or peroxides or in the presence of light with single oxygen resulting in the consumption of oxygen. The antioxidants are often mixed with the food and not incorporated in the packaging

Table 22.3 List of nanomaterials used in packaging industries

S. no.	Nanomaterials	Use in packaging	References
1	Silver	• Antibacterial agent • Nanosensors based on its surface plasmon resonance	Li et al. (2017), Busolo et al. (2010), Rvspayeva et al. (2018), Tripathi et al. (2018)
2	Zinc oxide	• Antibacterial agent • UV-protecting agent • Reduces oxygen permeability	Coralia et al. (2018), Emamifar et al. (2011)
3	Titania	• Photocatalytic agent • Antibacterial agent • UV-protecting agent • Oxygen scavengers	Coralia et al. (2018), Hoseinnejad et al. (2018), Tulsyan et al. (2017)
4	Cellulose	• Imparts strength to the films • Reduces oxygen and water vapor permeability	Vigneshwaran et al. (2011), Fortunati et al. (2013)
5	Chitosan	• Antibacterial agent	Ouattara et al. (2000), Cruz-Romero et al. (2013)
6	Clay	• Reduces oxygen and water vapor permeability • Improves the strength of films	Busolo and Lagaron (2012), Majeed et al. (2013), Goh et al. (2016)
7	Graphene	• Antimicrobial agent • Improves the strength of films • “smart” labels or tags	Sundramoorthy and Gunasekaran (2014), Goh et al. (2016), Merritt et al. (2018), Torres-Giner et al. (2018)
8	Silica	• Reduces the oxygen and water vapor permeability	Liu et al. (2012), Bang and Kim (2012), Venkatesan and Rajeswari (2016)
9	Lignin	• Antioxidant and antibacterial • Hydrophobicity • UV light absorption capacity	Domenek et al. (2013), de Azeredo et al. (2018), Yang et al. (2016, 2018)
10	Selenium	• Antioxidant agent • Antibacterial property	Hoseinnejad et al. (2018), Vera et al. (2016)

material. Commonly used antioxidants are butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbic acid, vitamin A, β-carotene, tocopherols, etc., (Brody et al. 2001; Gómez-Estaca et al. 2014).

22.2.1.3 Enzymatic Oxidation

Enzymatic oxygen scavenging systems are more expensive than iron-based systems, due to the cost of enzymes used for the oxygen-scavenging purpose. These systems involve use of enzymes like glucose oxidase which reacts with a substrate to scavenge oxygen. The use of enzymatic oxidation systems is limited due to their high sensitivity to temperature, pH, water activity, and the solvent or substrate present in the sachet (Cichello 2015; Mirabelli et al. 2018).

22.2.2 Carbon Dioxide Emitters and Scavengers

Carbon dioxide (CO_2) is known to have microbiological inhibitory effect in modified atmosphere packaging. Relatively high levels CO_2 (60–80%) prolong the shelf life of product by suppressing microbial growth on surfaces (Mane 2016; Sun et al. 2017). Oxygen-free environment alone is not enough to retard the growth of microorganism; therefore, a complementary approach to O_2 scavenging is required in the form of CO_2 generation or emission system. As the permeability of CO_2 is three- to fivefold higher than that of O_2 in most packaging films, it must be continuously produced to maintain the desired concentration within the package (Prasad and Kochhar 2014). High CO_2 levels, however, facilitate changes in the taste of product, thus CO_2 emitters can be used only in certain products such as fresh meat, poultry, fish, and cheese packaging. CO_2 emitters are often used with O_2 scavengers. They are mostly based on ferrous carbonate or a mixture of ascorbic acid and bicarbonate. The combined use of O_2 scavenger and CO_2 emitter is desirable to prevent the collapse of packages containing oxygen scavengers. These systems are also used in the packaging of products like peanuts and potato crisps, for which the volume of the package and its visual appearance are important (Wyrwa and Barska 2017). In such systems, bi-functional sachets are used, wherein O_2 scavenger absorbs the oxygen which is directly replaced by the same volume of carbon dioxide produced by CO_2 emitter. Iron carbonate(II) and metal halide are used as a catalyst in this type of systems (Cichello 2015).

Although CO_2 possess an antimicrobial activity, excess of CO_2 accumulation in a package may have a detrimental effect on the quality of the product and/or the integrity of the package particularly in the case of CO_2-producing foods such as fermented foods and fresh produce. In such products, active packaging systems containing CO_2 scavengers are beneficial. CO_2 is usually removed by placing calcium hydroxide or calcium oxide embedded in silica gel in suitable porous sachets inside packaging (Sung et al. 2013). The packages containing fermented vegetables like cabbage and onion produce CO_2 when packed even at cold storage. This results in pressure built up, swelling and even bursting of the package, thus decreases shelf life of the products. Zeolite is often used to adsorb CO_2 effectively to avoid pressure built up and to reduced swelling of the package (Lee et al. 2001). In roasted coffee, due to Strecker degradation reaction between sugars and amino acids, excess of CO_2 is produced which along with oxygen can be scavenged by a mixture of iron powder and calcium hydroxide (Floros et al. 1997).

22.2.3 Ethylene Scavengers

The control of ethylene during the storage of fresh produce is of key importance in prolonging the post-harvest life (Terry et al. 2007). Even a very low concentration of ethylene accelerate ripening, soften and degrade the chlorophylls, and inevitably lead to deterioration of fresh or minimally processed fruits and vegetables. Ethylene scavengers extend the shelf life of fruits or vegetables by slowing down their respiration rate and thus the ripening. The most commonly used ethylene scavenger is potassium permanganate ($KMnO_4$) embedded in silica gel which oxidizes ethylene to carbon dioxide and water. The oxidation of ethylene changes the color of $KMnO_4$ from purple to brown, and thus indicates its residual ethylene-absorbing capacity. The main disadvantage of $KMnO_4$ is toxicity; therefore, it is packed with silica gel in sealed sachets, excluding the possibility of direct contact with the product. The mechanism of action of other ethylene scavengers is based on their ability to absorb ethylene, alone or with any oxidizing agent. The examples of other ethylene scavengers are activated charcoal, bentonite, and aluminosilicates, i.e., zeolites, palladium chloride, etc. At high relative humidity, activated carbon with palladium chloride as a catalyst shows higher ethylene adsorption capacity than permanganate-based scavengers (Prasad and Kochhar 2014). Commercially, the ethylene-scavenging systems are available in the form of separate sachets or they are embedded in a polymeric material as finely powdered minerals (Wyrwa and Barska 2017).

22.2.4 Ethanol Emitters

Ethanol is mostly used as potential vapor phase inhibitor in medical and pharmaceutical packaging applications. Ethanol prevents intermediate moisture foods, cheeses, and bakery products from microbial spoilage and reduces the rate of staling and oxidative changes. An ethanol emission technology was originally developed in Japan, whereby fine inert food-grade ethanol powder is encapsulated inside a sachet. To maintain the preservative effect, the level of ethanol content into the packaging headspace is monitored by control release of encapsulated ethanol vapor. The rate of vapor release can be tailored by controlling the permeability of the sachet (Mane 2016; Mu et al. 2017).

22.2.5 Moisture Absorbers

The moisture content or humidity inside the package is of key importance to guarantee high quality of food. Excess moisture is a major cause of food spoilage. In many packed foods, especially fruits and vegetables, temperature difference within or outside the package often causes condensation of moisture. The presence of water droplets or too much moisture inside the package facilitates microbial growth and shortens product shelf life, also worsens package appearance. Moisture absorbers/scavengers are an effective tool for controlling water content in food packaging and thereby maintaining food quality and extending shelf life. Moisture absorbers are generally divided into two categories:

a. Sachets or pads The simplest moisture absorbers are sachets/pads filled with absorbing materials such as: silica gel, zeolites, calcium oxide, activated clay, propylene glycol, cellulose fibers, or sodium chloride. The best-known moisture absorbers are silica gels, which can absorb up to 35% of their own weight in water and can maintain the water activity down to below 0.2 (Powers and Calvo 2003). Zeolites can absorb water up to 24% of their weight and can also remove odors when dry (Panda and Shetty 2018). Sachets filled with propylene glycol or cellulose fiber pads are often used in contact with meat, poultry, and fresh produce within a package (Gaikwad et al. 2018).

b. Desiccating films These absorbers are made from synthetic polymers, in the structure of which desiccants are embedded. The commonly used desiccants are glucose solutions encapsulated between water vapor permeable films (not water permeable) (Brody et al. 2001) and water adsorptive polymers (Hurme 2002) like sodium polyacrylate as well as zeolites. The use of nanoparticles as moisture absorbers in food packaging are listed in Table 22.3.

22.2.6 Antimicrobials

The faulty/defective packaging (ruptured seal, puncture, dents, etc.) and inadequate processing may cause microbiological contamination of packaged product. Antimicrobial active packaging is a relatively new approach to control the microbial spoilage of foods. Antimicrobial packaging includes systems such as sachets or mats with volatile antimicrobial compounds, antimicrobials substances embedded in the polymer structure, antimicrobials applied to the polymer surface, antimicrobials immobilized on the polymer using ionic and covalent bonds, packaging films with inherent antimicrobial properties (e.g., chitosan films), etc. A variety of antimicrobial compounds is being used to inhibit the growth of microorganisms that can lead to the deterioration of foods. The volatile antimicrobial packaging is most commonly used because they can penetrate most of the food matrix and the direct contact of polymer with food is not required. Some of the examples of volatile antimicrobial compounds are chlorine dioxide, plant extracts, sulfur dioxide, essential oils, carbon dioxide, and allylisothiocyanate (Prasad and Kochhar 2014). Chlorine dioxide has proven record of high effectively not only against bacteria and fungi but also against viruses. It can exist in gaseous, liquid, or solid form and used mainly in packaging of meat, poultry, fish, dairy products, confectionery, and baked goods (Coma 2008). Sulfur dioxide is the most effective material for controlling spoilage of grapes. However, there may be chances of bleaching of grape skin and some sulfur dioxide may remain on grapes. Antimicrobial packaging containing nonvolatile compounds is another way of tackling the problem of microbial growth. These antimicrobials need to be in direct contact with the food to be active. Many preservatives such as ascorbic acid, benzoic acid, propionic acid and its salts, silver ions, bacteriocins (nisin & pediocin), enzymes (lysozyme), natural spices, etc., are added to plastic films as nonvolatile antimicrobials (Ouattara et al. 2000). The commercially available antimicrobial packaging systems are based primarily on substances containing silver. One of the first inorganic compounds, which is based on silver, is Zeomic®. It allows to control the growth of Gram-positive and Gram-negative bacteria as well as development of fungi. Moreover, compared to organic of antimicrobial substances, it shows good resistance to high temperature (Wyrwa and Barska 2017). Table 22.3 summarizes the use of nanoparticles in active packaging for antimicrobial purpose.

22.2.7 Flavor and Odor Absorber/Releaser

The release of essences/aroma and removal of off-flavors/odors are both beneficial for maintaining the original taste and flavor of the packaged fresh produce during storage. Active packaging containing flavor/aroma releaser masks unpleasant and bothering odors. They help to increase the desirability of the food to the consumer and to enhance the aroma of food product when the package is opened. The gradual release of flavors can offset the natural loss of taste or smell of products with long shelf lives (Almenar et al. 2009). However, currently, most aroma-releasing products are applied in plastic products for non-food applications only. The fragrances incorporated into packaging film in order to mask unpleasant odors produced during plastic processing should be thermally stable. A large percentage of fragrance oils are lost during the processing and the final films usually contain very less (about 0.2%) aroma compounds (Brody et al. 2001). The fragrance concentrates such as pine, lemon, and baby powder smells are generally used in bathroom and kitchen trash liners. In food applications, some coatings for sausages that contain spices and flavors are developed. An incorporation of aroma compounds into films of silica gel, ethylene vinyl alcohol, polyvinyl chloride, etc., also has been attempted. However, these films often have poor mechanical flexibility and short fragrance life. The main aim of odor absorbers is to obviate the potentially adverse effects of confinement odors as well as to obviate the effects of odors developed in the package materials themselves. The absorption of unpleasant aromas and flavors includes removal of amines produced during the oxidation of protein-rich foods like fish, removal of aldehyde/ketone compounds produced from lipid oxidation or anaerobic glycolysis, removal of sulfurous compounds like hydrogen sulfide from protein/amino acid breakdown as well as removal of bitter-tasting components like limonin in fruit juices (Svensson 2004). These odors are confined gas-barrier packages, thus releases unpleasant smell on opening of the package even if the food product is still safe to eat.

The amines can be removed by reaction with acidic compounds like citric acid, ascorbic acid, ferrous salt, and other organic acids incorporated in the packaging film. Zeolites, cyclodextrins, and activated carbon are often used for the removal of lipid oxidation odors. Odor removal by activated carbon is both effective and inexpensive method. Antioxidants like butylated hydroxytoluene (BHT), Vitamin E are included in the polyolefin-processing additive package to prevent lipid oxidation in dry foods like snack, cereal, and bakery products. To extend the shelf life of fatty foods or the foods sensitive to oxidation, the promising concept is to use both vitamin E and aldehyde scavenger. In such systems, Vitamin E, which is an antioxidant, reduces the oxidation rate while the scavenger removes produced odorous compounds (Prasad and Kochhar 2014). The odors may be developed in the packaging material, especially during plastic processing like extrusion and molding. DuPont, USA, has developed silica-based OTC (odor and taste control) to remove odors produced due to oxidation plastic resin during processing (Brody et al. 2001).

22.2.8 Other Active Packaging Systems

Other active packaging systems mainly include self-heating/self-cooling packaging, self-venting packaging, and microwavable packaging. The self-heating/self-cooling packaging is an important application of packaging which includes the use of innovative insulating materials, self-heating and self-cooling cans or containers. In case of chilled foods, the fluctuation in temperature during storage and distribution is prevented by using special insulating materials like Thinsulate, which is a special nonwoven plastic with many air pore spaces. Another strategy used for withstanding temperature rises is to increase the thermal mass of the food package. Self-heating packaging, especially cans or containers for coffee, tea, and ready meals are being used for decades. They are usually made up of aluminum and steel and heated by an exothermic reaction. These reactions mainly involve mixing of water and calcium or magnesium oxide (Mane 2016). Self-venting packaging is a type of packaging that controls the pressure inside the pack, venting the gas when the required pressure temperature level is reached. Microwavable active packaging is designed to ameliorate the heating characteristics of food by shielding, field modification, and use of susceptors (Regier 2014). Microwave susceptor consists of Al or SS deposited on substrates like polyester film or on paperboard resulting in uniform heating, surface browning, and crisping (Biji et al. 2015).

22.3 Intelligent/Smart Packaging

Smart packaging is defined as the packaging system that undergoes autonomous micro-structural modulations as the course of dynamic changes in the environment. Smart materials have the capacity to control the interface property based on the ionic channels and bio-inspired surface motions (Zhu et al. 2015). While, the traditional food packaging is mainly for protection, communication, convenience, and containment (Paine 2012; Robertson 2006). The smart packaging concepts are based on useful interaction between packaging environment and the food to provide very good protection to the food.

The value chain responsible for handling the agricultural commodity starts from the farm to fork moving on to small traders, transported to wholesalers and then reaches consumer through the long retail chain. At each change of hand, unpredictable losses in quality and quantity take place. These losses can be minimized by various physical, chemical, and biochemical interventions. Appropriate packaging is an important post-harvest unit operation which can extend shelf life of the produce. Packaging is extensively used as a tool in food processing in extending shelf life by protecting food against physical, chemical, and biological damage and against the environmental changes. Traditionally, plastic bags, gunny bags, cardboard boxes, paper bags, glass and metal containers, etc., are commonly used to unitize and transport the food. But these packaging materials do not interact with the food and cannot control the physiological changes. These constraints give rise to a new concept of active and intelligent/smart packaging which offers numerous and innovative solutions for extending the shelf life or maintain, improve or monitor food quality and safety. As discussed before, active packaging is based on a deliberate interaction of the packaging with the food and/or its direct environment. It uses an integrated approach to ensure an improved usability of food products. Intelligent packaging uses indicators such as time–temperature, RFID indicators, microbial growth, product authenticity, and pack integrity for monitoring food quality. With further development, these technologies can be manipulated to aid in the preservation and quality retention of fresh and minimally processed fruits and vegetables and commercially processed and packaged foods.

22.3.1 Developments in Package-Food–Environment Interaction

Biosensors include the biological molecules and microelectronics used to measure blood glucose levels, pollutants in the environment and the foodborne pathogens. Food packaging is used to provide passive protection against environmental contaminations to improve the shelf life of the products. Unlike traditional packaging, active packaging is designed to interact with the contents of the surroundings. Active packaging systems increase the shelf life of processed foods and can be classified into adsorbing and releasing systems. Intelligent packaging is characterized mainly by its ability to monitor the condition of packaged food or the environment by providing signal about various factors during transportation and storage. Intelligent packaging includes time and temperature indicators, gas sensors, and ripening monitors. Development of newer nanomaterials will enable the development of better and new active and intelligent packaging. Such packaging provides great benefits to food industry to keep freshness, increase the shelf life of food and allows continuous monitoring to control the storage conditions from the place of production to consumption by the final consumer.

Food and beverage manufacturers use smart packaging for finished goods and products. This helps them to provide the indication about the storage life and quality of the stored product. Smart sensors aid significantly in the control and monitoring of various aspects like moisture, oxygen, temperature, and freshness of foods. Sensors may be electronic or as simple as an indicator (Fathima 2017). Intelligent systems can be categorized as (i) data carries including barcode, RFID, electronic article surveillance (EAS), and digital watermark, (ii) quality indicators such as freshness indicator and time–temperature indicator, (iii) sensors and (iv) others are organic light-emitting diodes (OLED) and hologram (Mlalila et al. 2016)

Smart packaging has been a trending topic for years now. Smart packaging refers to an improved packaging system having functional attributes to add benefits to the food. Smart packaging includes an integrated approach with mechanical, chemical, and electrical driven functions to ensure an improved usability of packed food. The important aspects of smart packaging include the indication of ‘use by dates’, usage of self-heating/self-cooling containers, incorporation of electronic displays to indicate the storage temperature & nutritional information of the packed products (Mahalik and Nambiar 2010).

It comes with many names—it can also be called intelligent packaging, interactive packaging, or active packaging—or combinations of these. Smart packaging is about clever ways to package a product that interacts with the product—for example, to control the growth of bacteria or fungi. The most common name for this type of packaging is active packaging. In food packaging, interaction between the packaging material and the product should normally be avoided or minimized. This intelligence adds an extra information function to the packaging, often in the form of sensors and communication features (with or without electronics). One example of this type of smart packaging is “sensor-enabled RFID tag”.

22.3.2 Smart Barcode Packaging

Smart packaging took a step forward recently with the availability of a software tool that enables brand owners to create digital identities for their products using the existing GS1 identifiers in universal product codes (UPCs), thus web enabling any product with a UPC. It also allows brands to insert those same GS1 identifiers into other codes, including quick response (QR) codes and near-field communication (NFC) tags. This creates a standardized data format that is understood by all systems and readers in a product's life cycle. This approach to coding promises simplified packaging design—by eventually eliminating multiple on-pack codes—while driving smartphone interactions between consumers and brands. Each product with a smart barcode has a web address, and by scanning the code, consumers can access information about the product and brand owner (Connolly 2018).

By scanning near-field communication (NFC) technology-based chips embedded inside the packaging, consumers can gain access to recipes, cooking instructions and the inspiration for products, offering a wider experience with much lot of information. This way of helping the customers by smart packaging could play a significant role in boosting the individual brand engagement. In a similar way, brands can use this technology to detect the time at which their products are nearing expiration date, helping customers to avoid food waste by prompting them to use the product within the specified time. As the technology develops, we could see smart fridges that can detect the consumer's buying habits or plan their weeks' worth of recipes around those products and quantities.

22.3.3 Intelligent Packaging

Intelligent packaging refers to the usage of packaging as an intelligent messenger system to monitor the status and provide the quality information of packed foods to consumers (de Kruift et al. 2002). Major indicators include temperature, microbial attack, product authenticity, and package integrity. Recently, freshness and leakage indicators are commercially available for monitoring the quality of food. High temperatures are often associated with food deterioration as a result of irreversible biochemical reactions combined with microbial growth (de Kruift et al. 2002). The pH and enzymatic changes in the product also give information about the quality of the packed food. The Vitsab TTI indicator^{TM} (Vitsab Sweden AB, Sweden) measures the enzymatic reactions that could subsequently cause the pH change of product. The package contains the Vitsab TTI indicator window that indicates the difference between acceptable and distasteful product. The proven applications of nanomaterials in packaging industries are given in Table 22.3. Hydrogels can also present a conformation that allows their use in the packaging system to control the humidity generated by the food products. Also, the incorporation of nanomaterials into the hydrogels can grant them antibacterial activity (Batista et al. 2019).

22.4 Conclusion and Prospects

With the newer developments in the field of nanotechnology, various options of nanomaterials are available to use in food packaging system. Based on the requirement and other issues like eco-friendliness, toxicity level and biodegradability, and efficient nanosystem should be chosen for use in the food-packaging industry. Though metal and metal oxide nanoparticles are very efficient, moderately efficient bio-polymeric nanosystems like cellulose, chitosan, and lignin show prospects in terms of safety and eco-friendliness. Further research and developmental efforts are required to understand the effect of nanomaterials in the wasted nanocomposite films and the methodologies to be developed for proper treatment and disposal.

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Chapter 23
Sensors for Food Quality Monitoring

Nidhi Chauhan, Utkarsh Jain and Shringika Soni

Abstract Recently, there are gradually increasing demands of rapid, highly sensitive, and very selective methods in food safety and environmental monitoring. In response to this concern, conventional and nanotechnology-based biosensors have arisen as very effective and promising tool in analytical approach. It results in accurate chemical data in no time with cost-effective manner. This chapter presented herein aims to illustrate the type and principle of biosensors and their applications in food and environment monitoring. After briefly reviewing the different types of bio-elements (enzyme, antigen, antibody, DNA, aptamers, microbial cells) and transducers (electrochemical, optical, thermal, and mass-based), we have summarized different combinations of different receptors and transducers to design effective biosensors. Later in this chapter, we have elaborated the use of conventional biosensors as well as nanobiosensors in (1) quantitative detection of foodborne microorganism in eatable items, (2) pesticide detection in agriculture crops and environment, (3) toxin detection in food and water resources, and (4) xanthine and polyphenol detection in food, and alcoholic and non-alcoholic beverages. This chapter further tries to briefly summarize commercially available biosensors along with their manufacturer detail in food and environment monitoring. At last, conclusion, future challenges, and perspectives of biosensor in food quality management were explained in detail to give a strong basis for the further research in this area.

Keywords Biosensors · Food quality · Nanobiosensors · Foodborne disease · Pesticide · Toxin · Xanthine · Polyphenol

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23.1 Food Quality Monitoring: What and Why?

A food quality is generally referred to pathogen-free food and maintained nutritional quality for consumers. The concern for food quality was first originated in the nineteenth century; however, it remains a major global challenge. Maintaining the clean resources, food quality, and protecting the climate are difficult till date, while the population of humans and pathogens are also increasing in the same degree. Foodborne disease (FBD) is a very common and crucial global condition. The US Centers for Disease Control and Prevention reported that one out of six people, approximately 48 million people, get sick per year, 128,000 are hospitalized, and an average of 3000 people lost their life due to FBD in the USA (Centers for Disease Control and Prevention 2011; Yasmin et al. 2016). Even in India, Union Health Ministry's Integrated Disease Surveillance Program (IDSP) has reported about 100 million cases of FBD in 2011, but this is almost certainly an underestimation due to the lack of accurate estimates and the available surveys (Kristkova et al. 2017). Due to economic and population growth as well as urbanization, FBD can rise to 150–177 million from 100 million till the year 2030 (Kristkova et al. 2017). That means, one out of nine people in India may get sick till the year 2030 by FBD (Kristkova et al. 2017). The most common FBD pathogens are *Campylobacter* spp., *Listeria monocytogenes*, *Salmonella* spp., and *Escherichia coli* O157:H7 (Alocilja and Radke 2003; Chemburu et al. 2005). These pathogens result in recurring intestinal inflammation, chronic kidney diseases, mental disability, reactive arthritis, blindness, and even death (Hoffmann et al. 2015). Other allergens and chemical contaminations like toxins, pesticides, heavy metals, veterinary drugs/antibiotics, and packaging materials/food contact materials also reported to destroy the food quality and impact the human health (Regueiro et al. 2015; Gaonkar and McPherson 2016; Multer et al. 2017; Mie et al. 2017). The pesticides also reported widely distributed toxic chemicals in food and crops that affect GABA receptor channels, mitochondrial complexes, protein synthesis, and acetylcholinesterase enzyme (Costa 2008). The literature reported the death of approximately 800,000 people due to pesticides-loaded food consumption since the green revolution and 20,000 people are dying every year since then in developing countries (Abdou and Hend 2018). Agricultural predominance society of India has more than 125 pesticides industries and more than 500 pesticides formulation. Tons of DDT, hexachlorocyclohexane, and pentachlorophenol were in use every day that lead to the contamination of food and health problems (Abdou and Hend 2018).

Therefore, with the promotion of food safety announcement by WHO "from farm to plate (and everywhere in between) make food safe" on World Health Day 2015, there is an urgent need to correctly identify the source of food contamination to control the FBD and maintain food quality. The food industries need to follow the standards set by national or local authorities during production, handling, storage, processing, and distribution of the food material. They evaluate the food quality through several periodic chemical and microbiological analyses including chromatography, electrophoresis, spectrophotometry, titration, and others assays for further identifications (Qu et al. 2015; Fu and Ying 2016; Stachniuk and Fornal 2016; Nielsen 2017; Cutillas et al. 2018; Barbosa et al. 2019). These conventional methods are expensive, are time-consuming, need trained operators, and sometimes require extra steps to get correct results. Therefore, food industries and consumers require quick, affordable, and nondestructive methods to check the freshness and contamination-free food. For cheap and continuous monitoring with fast response time, sensors may be used with advantages. Recently, biosensors drag attention as an alternative to ease the analysis in routine of industrial food products. It can be used in the packaging, e.g., biosensor-based smart packaging, for carrying away food products (Kuswandi et al. 2011; Thakur and Ragavan 2013), or to check the quality of food like transportable kits (Bülbül et al. 2015; Yasmin et al. 2016; Dragone et al. 2017); both will be elaborated later in this chapter.

23.2 Biosensors

According to International Union of Pure and Applied Chemistry (IUPAC), biosensors can be summarized as self-contained integrated device to measure specific quantitative or semiquantitative biological reactions by generating electrical, thermal, or optical signals (Thévenot et al. 1999; Evtugyn 2016; Miyazaki et al. 2018; https://goldbook.iupac.org/html/B/B00663.html). The first idea for oxygen probe was designed in the year 1956 by Professor. Leland C. Clark (1956). Later, he designed the glucose oxidase-encapsulated oxygen probe electrochemical sensors in a Conference at the New York Academy of Sciences in the year 1962 (Clark and Lyons 1962). From then, many biosensors are developed for several biological and chemical samples, but the market ratio of biosensors for food quality measurement is very low.

23.2.1 Principle of Biosensor

The epithet “Biosensor” symbolizes a blend of two building blocks: bio-element and sensing element. Bio-element is a receptor that acts as sensor, and sensing element is a transducer that transmits the signals via thermal, electrical, or light reactions (Thakur and Ragavan 2013; Yasmin et al. 2016). When a specific bio-element reacts with a specific analyte, a physicochemical reaction will occur on the surface of transducer and results into visible output (as color change) or detection can be done via computer databases (Perumal and Hashim 2014; Eggeling et al. 2015). A biosensor can be designed based on their binding specificity to specific target and proper immobilization method (Singh et al. 2013). Immobilization is the process of proper attachment of biological component to the transducer without changing the activity of target molecule (Zhao and Jiang 2010; Yasmin et al. 2016). Performance and working of all these biosensors are based on its sensitivity, reproducibility, portability, high noise ratio, appropriate storage

Fig. 23.1 Types of receptors in biosensors (adopted from Thakur and Ragavan 2013)

condition, response time, and easy procedure to do tests (Ronkainen et al. 2010; Thakur and Ragavan 2013). The different types of receptors and transducers that are available are shown in Figs. 23.1 and 23.2.

Based on receptors, biosensors can be classified as immunosensors, DNA sensors, microbial sensor, and enzymatic sensor. The different bio-recognition elements like antigen (in case of immunosensor), DNA/RNA probe (in case of DNA biosensor), microbes (in case of microbial sensor), and enzyme substrate (in case of enzymatic sensor) bind to different transducers (electrochemical, optical, thermal, and piezoelectric) in different combinations to achieve the result of interest. Currently, enzyme-based electrochemical biosensors are prominent in the market for medical diagnosis, food quality, and environmental pollutant detection, but the high sensitivity and very low detection time were repeatedly reported in nanotechnology-based biosensors. Nanobiosensors may play a vital role in biosensor field in the future.

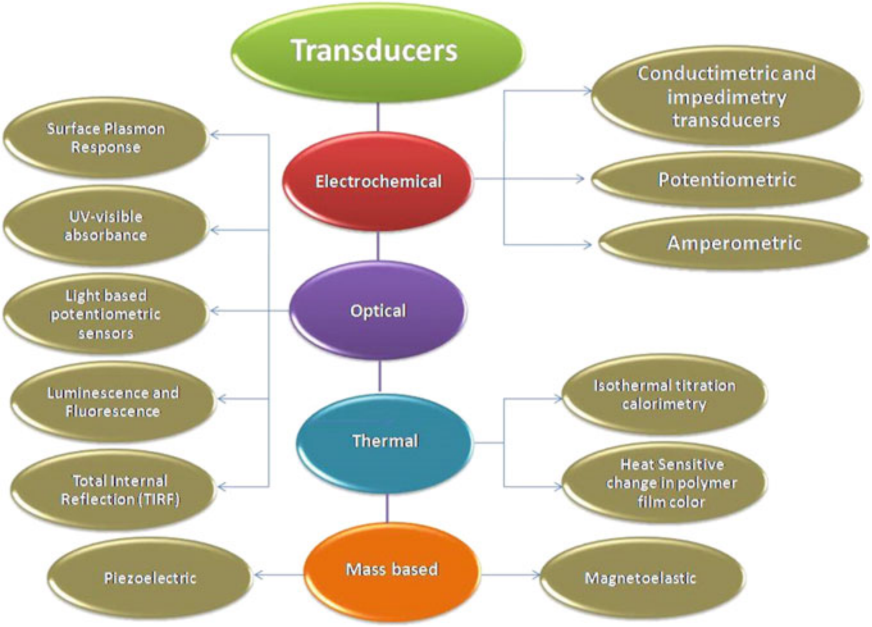

Fig. 23.2 Types of transducers in biosensors (adopted from Thakur and Ragavan 2013)

23.2.2 *Electrochemical Biosensor*

An electrochemical biosensor is an integrated analytical device to detect the samples based on electrochemical signals generated during biochemical reaction on transducers (Thakur and Ragavan 2013; Yasmin et al. 2016; Naik et al. 2017). Because of their transduction methods, electrochemical sensors are classified into potentiometric (potential difference measurement between indicator and reference electrode), amperometric (current measurement in electrochemical reaction), and conductimetric (measures change in conductivity during biochemical reaction) (Mello and Kubota 2002; Thakur and Ragavan 2013; Yasmin et al. 2016; Naik et al. 2017). Currently, DNA, antibody, and hybrid bio-receptor-based electrochemical biosensors were reported very specific and reliable technique in food quality detection. They were used in toxin detection (Bonel et al. 2011; Yu et al. 2015a, b; Byrne et al. 2015), microorganism detection (Ligaj et al. 2014; Izadi et al. 2016; Cinti et al. 2017; Arora 2018), and pesticide detection (Zhu et al. 2015; Zhang et al. 2018) (Tables 23.1, 23.2, 23.3, 23.4).

Table 23.1 Biosensors in food pathogen detection

S. no.	Pathogen	Biosensor	Samples	Detection limit	Response time	References
1	*S. pullorum and S. gallinarum*	Electrodeposited AuNP-based electrochemical immunosensor	Egg and chicken meat	3.0×10^3 CFU/mL	–	Fei et al. (2015)
2	*V. parahaemolyticus and S. typhimurium*	CNP-conjugated QD-based aptamer biosensors	Shrimp and chicken breasts	25 CFU/mL and 35 CFU/mL	–	Duan et al. (2015)
3	*E. coli* O157:H7 and *Salmonella* sp.	pCBAA brushes-based SPR biosensor	Cucumber and hamburger	57 CFU/mL and 17 CFU/mL; 7.4×10^3 CFU/mL and 11.7×10^3 CFU/mL	<80 min	Vaisocherová-Lísalová et al. (2016)
4	*V. parahaemolyticus*	DNA hybridization-based portable electrochemical biosensor	Seafood (*Anadara granosa*)	2.16 pM	–	Nordin et al. (2017)
5	*E. coli O157:H7* (*O157:H7*), *S. enteritidis*, *and L. monocytogenes*	Multichannel SPR immunosensor	Chicken	25 CFU/mL, 8.4 CFU/mL, and 23 CFU/mL	–	Zhang et al. (2017a, b)
6	*E. coli O157:H7*	MEMS-based impedance immunosensor	–	13 CFU/mL	30 min	Abdullah et al. (2017)
7	*Salmonella* sp.	MEMS-based impedance immunosensor	Turkey	7 CFU/mL	30 min	Jasim et al. (2017)
8	*S. enteritidis*	Nanocomposite-associated smartphone-based immunosensor	Milk, cheese, and water	1 CFU/mL, 1 CFU/mL, and 1 CFU/gm	–	Zeinhom et al. (2017)
9	*E. coli and S. aureus*	UCNP-conjugated antibody biosensor	Pork and milk	13 CFU/mL and 15 CFU/mL	–	Zhang et al. (2017a, b)
10	*E. coli* O157:H7	Magnetic nanoparticles and QD-based fluorescent immunosensor	–	14 CFU/mL	60 min	Xue et al. (2018)
11	*V. parahaemolyticus*	AuNP-based aptasensor	Oyster	10 CFU/mL (from naked eyes)	~5 min	Wu et al. (2018)

Table 23.2 Biosensors in pesticide detection

S. no.	Pesticide	Biosensor/biosensing method	Samples/crop	Detection limit	Response time	References
1	Phoxim and chlorpyrifos	AChE-coated MWCNT-based piezoelectric biosensor	Radishes	–	–	Shang et al. (2011)
2	DDVP	AChE-coated QD	Apple	4.49 nM	–	Meng et al. (2013)
3	Organophosphorous pesticides (OP) paraoxon	AChE-immobilized CNT amperometric biosensor	Vegetable samples (cabbage, celery, onion, and carrot)	0.08 nM	10 min	Yu et al. (2015a, b)
4	Carbaryl and monocrotophos	AChE-immobilized ionic liquid-functionalized graphene amperometric biosensor	Tomato juice samples	5.3×10^{-12} M	5 min	Zheng et al. (2015)
5	Organophosphate	AChE-coated graphene QDs-based biosensing	Water	0.778 µM	–	Sahub et al. (2018)
6	Carbofuran	Impedance electrochemical immunosensor	Tomatoes, cabbage, and lettuce	10^{-1} ng/mL	–	Liu et al. (2015a, b)
7	Metolcarb	MWCNT-PAMAM-based piezoelectric immunosensor	Apple and orange	0.019 mg/L	–	Pan et al. (2013)
8	Chlorpyrifos	Polymer–clay nanocomposite-based AChE biosensor	–	0.448 mg/L	–	Sarkar et al. (2017)
9	Tetrachlorvinphos	HRP-H_2O_2-based optical biosensor	Water	4.0×10^{-7} to 4.0×10^{-6} mol/L	–	de Marcos et al. (2014)
10	Atrazine	Ag-Ab recognition-based SPR biosensor on AuNP	Maize	1.0–15.6 ng/mL	–	Liu et al. (2015a, b)

Table 23.3 Biosensors used in toxin detection

S. no.	Toxin	Biosensor/biosensing method	Samples	Detection limit	References
1	Botulinum neurotoxin A (BoNT/A)	Graphene oxide-based FRET biosensor	Skimmed milk and apple juice	1 fg/mL–1 pg/mL	Shi et al. (2015)
2	Botulinum neurotoxin	Graphene nanocomposite-based impedimetric immunosensor	Milk and serum	0.11 pg/mL	Afkhami et al. (2017)
3	TcdA and TcdB	Electrochemical impedance immunosensors	Shellfish	0.61 pg/mL and 0.60 pg/mL	Zhu et al. (2015)
4	DSP toxin	Human cancer cell-based impedance biosensors (CIBs)	Seafood	3.3–10.4 μg/L	Zou et al. (2016)
5	Fumonisin B1 and deoxynivalenol	Electrochemical immunosensor	Corn	4.2 ppb and 8.6 ppb	Lu et al. (2016)
6	Aflatoxin B1	Poly (3,4-ethylenedioxythiophene)-AuNP-based electrochemical immunosensor	Maize	0.0045 ng/mL	Sharma et al. (2017)
7	Saxitoxin, decarbamoyl saxitoxin, gonyautoxin GTX5, and C1 and C2	Potentiometric chemical sensors	Seafood	0.25–0.9 μmol/L for saxitoxin and decarbamoyl saxitoxin, and from 0.08 to 1.8 μmol/L for GTX5 and C1 and C2	Ferreira et al. (2018)
8	Okadaic acid	Smartphone-based system using cell viability biosensor (CVBS)	Seafood	10–800 μg/L	Su et al. (2017)
9	Ochratoxin A	QCM-D biosensor	Red wine	0.16 ng/mL	Karczmarczyk et al. (2017)
10	Cyanotoxins	Aptamer-based microcantilever array sensor	Water	1–50 μg/mL	Zhang et al. (2018)

Table 23.4 Biosensors used in xanthine/polyphenol detection

S. no.	Xanthine/ polyphenol	Biosensor/biosensing method	Samples	Detection limit	Response time (s)	References
1	Xanthine	Amperometric biosensors based on carboxylated MWCNTs-metal oxide nanoparticles-7,7,8,8-tetracyanoquinodimethane	Coffee	3.6×10^{-7} M	–	Dalkıran et al. (2017a)
		Glassy carbon electrode-based electrochemical biosensor	Fish	2×10^{-4} nM	10	Dalkıran et al. (2017b)
		RB-capped TGA/GNPs-based fluorescent biosensor	Coffee	10.1 nM/L	–	Menon and Kumar (2017)
		MNPs-/c-MWCNT-based sensor	Fish	0.05 mM	3	Jain et al. (2016)
		CdO-NPs- and MWCNTs-based sensor	Fish	0.05 mM	4	Jain et al. (2015)
2	Hypoxanthine (Hx)	Electrochemiluminescence biosensor	Human serum	0.007 nM	–	Zuo et al. (2018)
3	Catechol	Phospholipid, phthalocyanine, and AgNP-based biosensor	Green tea	0.87 µM	–	Alessio et al. (2016)
		Optic laccase biosensor	–	0.04 mM	–	Bilir et al. (2016)
4	Catechol and catechin	Nitrogen-doped MWCNT (Lac/CNx-MWCNT) and on graphene oxide (Lac/GO)-based biosensor	Wine	10^{-8} mol/L	–	Aguila et al. (2015)
5	Polyphenol	Amperometric biosensor	Tea leaves, alcoholic beverages, and water	0.05 µM	30	Narang et al. (2013)

23.2.3 Optical Biosensor/Optodes

These biosensors work on the principles of absorption, internal reflection, fluorescence, surface plasmon resonance (SPR), luminescence, or light scattering spectroscopy during the biochemical reaction (Thakur and Ragavan 2013; Korotkaya 2014; Meshram et al. 2018). These biosensors are also called as *optodes* as they look like electrodes that work on the light system (Thakur and Ragavan 2013). SPR is the major technique in optical biosensor in the food industry. Like electrochemical biosensor, optodes also integrate with enzyme, antigen, antibody, microbial cell, DNA, or aptamers to enhance the biosensor's efficiency to detect food contamination detection (de Marcos et al. 2014; Shi et al. 2015; Ko and Grant 2006; Bilir et al. 2016; Zuo et al. 2018) (Tables 23.1, 23.2, 23.3, 23.4).

23.2.4 Mass-Based Biosensors

The piezoelectric crystal-based biosensor is the main class of mass-based biosensors, though these are less frequently used than electrochemical and optical biosensors in food industries. The piezoelectric biosensors analyze the samples because of change in mass during biochemical reaction when electrical current at fixed frequency is applied (Velusamy et al. 2010; Yasmin et al. 2016). Nowadays, rather than using conventional piezoelectric biosensor, nanotechnology-based piezoelectric biosensors are more in use to detect food and environment contamination (Shang et al. 2011; Pan et al. 2013; Marrazza 2014; Nikoleli et al. 2018; Spychaj et al. 2018) (Table 23.1, 23.2, 23.3, 23.4).

23.2.5 Thermal Biosensor

Thermal biosensor analyzes the sample based on change in heat over time in a biochemical reaction on transducer (Mello and Kubota 2002; Lim and Ahmed 2016). Their use in food quality analyses is limited due to its low selectivity, heat loss in irradiation, or conduction/convection during biochemical reaction and complex instrumentation in thermal biosensor design (Mello and Kubota 2002). Still, some food industries rely on this biosensor to ensure the food quality (Ramanathan et al. 1999, 2001; Mello and Kubota 2002).

23.2.6 Nanobiosensor

Over the past few decades, nanotechnology has revolutionized the field of biosensors to maintain food quality and improve public health. This is the just like conventional biosensors except for nanomaterial integration in biosensors to increase sensitivity, efficiency, and portability of device (Rai et al. 2012; Singh et al. 2017). These nanomaterials can be used as coating into biosensor device or in barcode for sealed food or conjugated with electrochemical or optical biosensors along with DNA, enzyme, microbial cells or antigen, antibody to ensure the food quality (Aguila et al. 2015; Jain et al. 2015, 2016; D'Souza et al. 2017; Singh 2017; Patel et al. 2018; Arora 2018) (Table 23.1, 23.2, 23.3, 23.4).

23.3 Biosensors in Food Quality Analysis

As the ratio of FBD is increasing globally, food safety is a primary goal and significant health concern in human population. Food safety needs to take care from handling to manufacturing, distribution, and consumption for the prevention of FBD and associated outbreaks. Primarily cause of biological hazards does not include change in organoleptic properties of food, but serious health issues can occur. Other than this, pathogenic FBD has long-term social and economic impact (Plata 2003). *Campylobacter* spp., *Listeria monocytogenes*, *Salmonella* spp., and *Escherichia coli* O157:H7 are the most common pathogens for FBD, but entero-hemorrhagic strains of *Escherichia coli* O111, O103:H25, O145, O26, O115, O128, and O104:H4, *Bacillus cereus*, *Clostridium botulinum*, *Bacillus anthracis*, *Clostridium perfringens*, *Mycobacterium bovis*, *Yersinia enterocolitica*, *Aeromonas* spp., *Shigella* spp., *Vibrio* spp., and viruses and protozoa are also reported in food transmitted illness (Alocilja and Radke 2003; Chemburu et al. 2005; Poltronieri et al. 2014; Yasmin et al. 2016). Other than these foodborne pathogens, several neurotoxins, mycotoxins, pesticides, xanthine, and polyphenols were also responsible for food spoilage and disrupt the human health. The traditional and conventional methods, like HPLC, spectroscopy, or ELISA, are time-consuming, expensive, and laboratory procedure. Biosensor may not only help in pathogenic food detection in no time, but it is also easily portable, quick, specific, and targeted approach.

From decades, there are so many biosensors in the market, but in this chapter, we will be focusing on biosensors used in food quality management. After the three generations of biosensors, nanobiosensors were used frequently for accurate and highly sensitive issues in the twenty-first century.

- *First generation:* It operates based on electrical response.
- *Second generation:* Specific mediators are used to improve response of transducers.

- *Third generation:* No mediator is directly involved, and reaction itself causes the response.
- *Nanobiosensors:* Nanoscale size biosensor.

23.3.1 Biosensors in Food Pathogen Detection

To cope up with increasing incidence of FBDs, more convenient, sensitive, and accurate technique like biosensors should be in-line to detect correct pathogen. The modified and nanotechnology-based electrochemical and optical biosensors are most commonly used in food pathogen detection. In recent years, nanobiosensors have hold its position at peak in foodborne pathogen detection and their combinations with other techniques improve the food quality detection in common public. Sandwich immunoassay-based biosensors were reported to overcome the issue of false-negative result that commonly happened in conventional biosensors. Fei et al. (2015) have modified screen-printed carbon electrode (SPCE) with electrodeposition of unlabeled antibody-coated magnetic nanoparticles and later synthesis sandwich via exposure of HRP labeled secondary antibodies to design electrochemical immunosensor for the detection of *S. pullorum* and *S. gallinarum* in egg and chicken. The extensive properties of carbon nanoparticles (CNPs), like zero-dimensional, uniform size distribution, good compatibility of biomolecules, and comparatively less complex synthesis procedure, opened a new door in the field of biosensors. In this direction, dual fluorescence resonance energy transfer (FRET)-based QD and amorphous CNP-conjugated aptasensors were designed to detect *V. parahaemolyticus* and *S. typhimurium* in shrimp and chicken breast samples with limit of detection of 25 CFU/mL and 35 CFU/mL, respectively (Duan et al. 2015). Similarly, a DNA hybridization-based portable electrochemical biosensor labeled with methylene blue (MB) was designed for *V. parahaemolyticus* detection in seafood with detection limit of 2.16 pM (Nordin et al. 2017). A rapid and highly sensitive AuNP-based aptasensor was also designed to detect *V. parahaemolyticus* in oyster sample in less than 5 min (Wu et al. 2018). Most common FBD pathogens, *E. coli* O157:H7 and *Salmonella* sp., were always a challenge in food safety. Recently, several biosensors were designed for their detection. Vaisocherová-Lísalová and his colleagues designed poly(carboxybetaine acrylamide) (pCBAA) brushes-based SPR biosensor for rapid and sensitive detection of *E. coli* O157:H7 and *Salmonella* sp. in complex foods like cucumber and hamburger samples (Vaisocherová-Lísalová et al. 2016). Similarly, surface-modified gold chip of SPR biosensors was converted into multichannel SPR immunosensor to detect *E. coli O157:H7* (*O157:H7*), *S. enteritidis, and L. monocytogenes* in chicken sample with limit of detection of 25 CFU/mL, 8.4 CFU/mL, and 23 CFU/mL, respectively (Zhang et al. 2017a, b). To improve the sensitivity, researchers focused on microelectromechanical systems (MEMS)-based affinity biosensors. This MEMS-based impedance immunosensor was reported in *E. coli* and

Salmonella sp. in turkey sample with limit of detection of 13 and 7 CFU/mL in less than 30 min (Abdullah et al. 2017; Jasim et al. 2017). A magnetic nanoparticle and QD-based fluorescent immunosensor was designed to detect *E. coli O157*:*H7* in 60 min with limit of detection of 14 CFU/mL (Xue et al. 2018). We have mentioned few examples of biosensors in FBD detection in Table 23.1.

23.3.2 Biosensors for Pesticide Detection

The use of pesticide is a necessary evil in today's agriculture world. These pesticides and insecticides not only affect food, but also pollute water and environment. Their correct detection is very difficult and time-consuming process. Therefore, while maintaining their selectivity and sensitivity, biosensors can play a vital role in rapid and accurate detection of pesticides in laboratories and via using portable detection kit. After the discovery of many biosensors, recently nanobiosensors are very much in use.

Acetylcholinesterase (AChE)-based electrochemical and optical biosensors along with nanomaterials like carbon nanotube (CNT), quantum dots (QD), graphene, and nanocomposites integration were used to detect different pesticides like paraoxon, carbaryl and monocrotophos, dichlorvos or 2,2-dichlorovinyl dimethyl phosphate (DDVP) and phoxim in eatable samples in less than 10 min (Shang et al. 2011; Meng et al. 2013; Yu et al. 2015a, b; Zheng et al. 2015; Sarkar et al. 2017; Sahub et al. 2018). These types of affinity biosensors along with nanomaterials increase the sensitivity of the devices and detect compound of interest. Chauhan et al. have designed several acetylcholinesterase (AChE)-immobilized AChE/Fe_3O_4/c-MWCNT/Au electrodes, porous gold-nanoparticle–$CaCO_3$ hybrid material-modified Au electrodes, ZnS and poly(indole-5-carboxylic acid)-modified Au electrodes, and Fe_3O_4 nanoparticle/multiwalled carbon nanotube-modified ITO-coated glass plate-based sensors for organophosphorus insecticide detection at nano level (10^{-9}) (Chauhan et al. 2011a, b; Chauhan and Pundir 2011, 2012). Other than these, multiwalled CNT (MWCNT)–polyamidoamine (PAMAM)-based piezoelectric immunosensor is used to detect metolcarb with detection limit of 0.019 mg/L (Pan et al. 2013). Later impedance electrochemical immunosensor was reported to detect carbofuran with detection limit of 10^{-1} ng/mL (Liu et al. 2015a, b). Marcos and team have designed an optical biosensor based on absorbance pattern of oxidized heme protein horseradish peroxidase (HRP) to detect tetrachlorvinphos in 4.0×10^{-7} to 4.0×10^{-6} mol/L linear concentration of water sample (de Marcos et al. 2014). Similarly, gold nanoparticle-conjugated SPR immunosensor was also reported to enhance the detection signals of atrazine in maize sample that can easily quantify 1 ng/mL (Liu et al. 2015a, b). Due to the sensitivity and accuracy along with facile method for pesticide or insecticide detection in agriculture, these biosensors are proved very feasible for in situ detection. Few examples are briefly described in Table 23.2.

23.3.3 Biosensors in Toxin Detection

A long range of natural and artificial toxin available in food and environment represents a big challenge when it comes to their accurate detection. The half-life of each toxin is different; it needs to be correctly detected on time in eatable items to prevent the potential deadly epidemic. Therefore, different neurotoxins, mycotoxins, and other toxins can be detected through biosensors. Currently, the second and third generations of nanobiosensors are present in the market for toxin detection.

The graphene-based fluorescence resonance energy transfer (FRET) biosensor was designed to detect botulinum in range of 1 fg/mL–1 pg/mL in milk sample (Shi et al. 2015). Similarly, graphene nanocomposite-based impedimetric immunosensor was also tested to detect botulinum toxin in milk and serum sample (Afkhami et al. 2017). Other modified electrochemical biosensors were used to detect fumonisin B1, deoxynivalenol, aflatoxin B1, diarrhetic shellfish poisoning (DSP) toxin, Clostridium difficile toxin A (TcdA) and toxin B (TcdB), saxitoxin, decarbamoyl saxitoxin, gonyautoxin GTX5, and C1 and C2 in food samples in very minute amount (Zhu et al. 2015; Zou et al. 2016; Lu et al. 2016; Sharma et al. 2017; Ferreira et al. 2018). With the advancement in these detection techniques, biosensors can also be associated with smart monitoring device for quick and correct toxin detection. Su et al. have designed smartphone-based biosensor to detect okadaic acid in seafood. The research team used HepG2 cells as sensing elements to specifically react with okadaic acid, and cell viability was checked through homemade iOS APP–iPlate Monitor in a smartphone (Su et al. 2017). This portable device could measure 10–800 μg/L toxins in sample. Similarly, quartz crystal microbalance with dissipation monitoring (QCM-D)-based immunosensors was designed to detect one of the highly toxic mycotoxins, ochratoxin A (OTA) in red wine sample (Karczmarczyk et al. 2017). Karczmarczyk et al. used quartz crystal microbalance transducer that measures change in frequency and dissipation-based signals, and secondary antibodies-conjugated gold nanoparticles generate and amplify adequate signals to detect OTA in range of 0.16 ng/mL. Due to environmental and economic concern of toxin detection, there are several researches focused on biosensor design, and few of them briefly mentioned in Table 23.3.

23.3.4 Biosensors in Xanthine/Polyphenol Detection

Purine derivative xanthine is derived from ATP hydrolysis of guanine and ultimately converts into uric acid that causes gout, hyperuricemia, preeclampsia, and xanthinuria in human (Dervisevic et al. 2017). It is also a good indicator for meat and fish spoilage to determine its freshness (Chu et al. 2014; Dervisevic et al. 2017). Therefore, several researches were focused to design biosensors to detect xanthine in eatable food items. Recently, chemically modified CNT-based electrochemical and optical nanosensors were designed. Dalkıran et al. (2017a) designed carboxylated amperometric biosensors conjugated with 7,7,8,8-tetracyanoquinodimethane metal oxide nanoparticles and coated with xanthine oxidase (XOD) to detect xanthine in coffee sample. Later, this team designed graphene (GR), Co_3O_4 nanoparticles, and chitosan (CH)-modified glassy carbon-based xanthine biosensor for fish sample in 10 s, whose limit of detection was 2×10^{-4} nM (Dalkıran et al. 2017b). To increase the sensitivity and detection limit of the xanthine biosensors, bioaffinity receptors were in use. One research focused on the rhodamine B-capped thioglycolic acid-functionalized gold nanoparticles (RB-capped TGA/GNPs)-based fluorescent xanthine biosensor. This sensing mechanism based on quenching of gold nanoparticle due to enzymatic degradation of xanthine in uric acid and fluorescence signals was analyzed in a coffee sample to quantify the xanthine (Menon and Kumar 2017). Similarly, magnetic nanoparticles (MNPs)-based carboxylated multiwalled carbon nanotube (c-MWCNT) and CdO-NPs-/MWCNTs-based reusable biosensors were designed to detect xanthine content in fish samples (Jain et al. 2015, 2016). In both studies, XOD was extracted from bovine milk and immobilized on modified MWCNT that quantify the xanthine in less than 5 s. Their sensitivity, quick response time, and reusable property make the biosensor unique.

Several other studies also focused on polyphenol detection in food samples. Phospholipid, phthalocyanine, and AgNP-based biosensor and optic laccase biosensor were designed to quantify catechol in coffee samples (Alessio et al. 2016; Bilir et al. 2016). Aguila et al. (2015) designed nitrogen-doped MWCNT (Lac/CNx-MWCNT) and on graphene oxide (Lac/GO)-based biosensor to detect both catechol and catechin in wine sample with detection limit of 10^{-8} mol/L. An amperometric biosensor was also designed to detect polyphenol in tea leaves, alcoholic beverages, and water (Narang et al. 2013). They used polyvinyl alcohol membrane-conjugated polyphenol oxidase which was mounted on gold-coated silver wire to quantify the polyphenol content in caffeine and alcoholic samples. After the globalization and high requirement of alcoholic and non-alcoholic beverages, the contamination-free products are on priority. Therefore, several researches are pointing to design very specific and sensitive polyphenol biosensors, and some of them are discussed in Table 23.4.

23.4 Commercially Available Biosensors for Food Safety Analysis

After the boom of biosensors in food industries and awareness in common public for food safety, the demand and requirement of the biosensors have been increased. Currently, more than 2000 biosensors are present in the market for food analysis, but these are limited to very short range of contamination detection. The 3M™ Corporation has developed several laboratories on chip device to detect *Salmonella* and *Listeria* in dairy product (www.nanosphere.us and http://www.3m.com/).

Neogen has designed isothermal amplification technology-based ANSR to detect *Salmonella* and *Listeria* (www.neogen.com), immunoassay with chromatography-based Reveal® test (www.neogen.com), DNA hybridization technology-based GeneQuence® assay to detect *Salmonella*, *Listeria*, or *L. monocytogenes* (www.neogen.com). The Analyte 2000™, Malthus systems, Bioflash, and ToxinGuard are few from the examples of the marketed biosensor for *E. coli* O157:H7 detection in food products (Sharma et al. 2013; Tatari et al. 2016; Antonacci et al. 2016). Similarly, BAX® System, Assurance®, and ToxinGuard are also used in the detection of *L. monocytogenes* in meat and eatable food products (Valderrama et al. 2016; Antonacci et al. 2016). There is a long list of the marketed biosensors in food industries, and we tried to summarize the detailed information of commercially available biosensors in Table 23.5.

23.5 Regulation in Food Quality Management: Indian Scenario

The need of food quality management has reached at its peak with gradually increasing population, food industries, and more globalization. After establishing the first global quality management system, ISO 9000 in Geneva, Switzerland, ISO 22000 international standard was developed to ensure the safety of food and health (Schoenfuss and Lillemo 2014). ISO 22000 integrates with Hazard Analysis and Critical Control Point (HACCP) system, Good Manufacturing Practice (GMP), General Principles of Food Hygiene (GHP), and Good Agricultural Practices (GAP) for more effective food safety management. These regulations are based on Codex Alimentarius (means *Food Code*). The codex is the collaborative effort of health and food body of United Nations, WHO, and Food and Agriculture Organization (http://www.fao.org/fao-who-codexalimentarius/en/). It is the collection of standards, guidelines, and codes of practice to ensure the safety of food and health. The European Food Safety Authority for European countries, Food Standards Australia/New Zealand for Australia and New Zealand, and the US Food and Drug Administration (USFDA) also help in maintaining the food quality from the manufacturing to long way till consumers get the food product. India food regulatory authority, FSSAI, is not only based on Codex Alimentarius, but it also integrated and harmonized the food safety regulation from other countries to some extent like USA and Europe.

The food quality in India is monitored by Food Safety and Standards Authority of India (FSSAI) under the aegis of Ministry of Health and Family Welfare (MoHFW), Government of India. They implement and enforce the food regulation under Food Safety and Standards Act, 2006 (FSS Act) that officially become effective in the year 2011 (http://www.fssai.gov.in/home/fss-legislation/food-safety-and-standards-act.html). This “umbrella law” is combination of *Vegetable Oil Products* (*Control*) *Order*, *1947*, *Prevention of Food Adulteration Act*, *1954*,

Table 23.5 Commercially available biosensors for food safety analysis

S. no.	Biosensor brand name	Manufacturer	Detection	Food/sample	References
1	Spreeta™	Texas Instruments Inc.	Ingredients, contaminations	Beverages	Sharma et al. (2013)
2	Analyte 2000™	Research International Ltd.	*E. coli* O157:H7	Hamburger	
3	Malthus systems	Malthus Instruments Ltd.	*E. coli* O157:H7, fungi, yeast	Shellfish	
4	Rapid Automated Bacterial Impedance Technique (RABIT)	Don Whitley Scientific Ltd.	Food pathogens	Vegetables	Tatari et al. (2016)
5	Bioflash system	TM Innovative Biosensors Inc.	*E. coli* O157:H7	Lettuce	
6	Diffractive Optics Technology (DOT™) sensor and DOT™ reader	Axela Biosensors, Inc.	–	Agricultural, environmental, and food and beverage sector	
7	Phage biosensor	Biophage Pharma Inc.	*E. coli* O157:H7, *Campylobacter*, *Salmonella*	Water	
8	CALM	Colifast A/S, Norway	Total *coliforms*, *E. coli*, *P. Aeruginosa*	Raw water, process water, wastewater	
9	aquaBio	ADASA, Spain	Total *coliforms* and *E. coli*	Drinking water, wastewater, bathing water	
10	ColiMinder	Vienna Water Monitoring (VMW) Solutions, Austria	Total *coliforms*, *E. coli*, or total bacteria	Sewage, surface water, and soon tested in drinking water	
11	Blusense Diagnostics ApS	Spin-off from DTU Nanotech, Denmark	Specific bacteria strains	Drinking water	
12	Icon HP	Beckman Coulter, USA	*H. pylori*	Water, food	Bahadır and Sezgintürk (2015)
13	ImmunoCard STAT! HpSA	Meridian Bioscience, USA	*H. pylori*	Water, food	
14	ToxinGuard	Toxin Alert, Ontario, Canada	*Salmonella* sp., *Campylobacter* sp., *E. coli* 0517, and *Listeria*	Plastic sealed food	Antonacci et al. (2016)
15	Food Sentinel System	SIRA Technologies, California, USA	Bacteria detection	Sealed food	
16	Assurance®	Neogen Corporation, USA	Enterohemorrhagic *E. coli* (EHEC), *L. monocytogenes*	Apple cider, cheese, beef, egg, liquid milk, nuts, pasta	Valderrama et al. (2016)
17	BAX® System	DuPont™, USA	*E. coli* O157:H7 MP, *L. monocytogenes*, *Salmonella*	Meat, fruits, vegetable, animal feed	

Fruit Products Order, *1955*, *Solvent Extracted Oil*, *De-Oiled Meal and Edible Flour* (*Control*) *Order*, *1967*, *Meat Food Products Order*, *1973*, *Edible Oils Packaging* (*Regulation*) *Order 1988*, *Milk and Milk Products Order*, *1992* (http://www.swaniti.com/wp-content/uploads/2015/06/Food-safety-in-India-1.pdf). Their regulation is framed under *Food Safety and Standards* (*Food Product Standards and Food Additives*) *Regulation*, *2011*, *Food Safety and Standards* (*Packaging and Labelling*) *Regulation*, *2011*, *and Food Safety and Standards* (*Contaminants*, *Toxins*, *and Residues*) *Regulations*, *2011*. With main headquarter in New Delhi, FSSAI has six regional offices, 14 referral laboratories, 72 state/UT laboratories, and 112 National Accreditation Board for Testing and Calibration Laboratories (NABL)-accredited private laboratories located throughout India. They have appointed 35 commissioners of food safety and more than 2000 food safety officers/food inspectors to ensure the food quality regulation implementation. Food industries or manufacturer need to apply for licensee to FSSAI if their product comes under standardized food products (SFP) categories. Based on the annual turnover, manufacturer can apply to FSSAI registration/license online on https://foodlicensing.fssai.gov.in/index.aspx.

- Below 12 lakhs annual turnover business: simple registration FORM A.
- 12–20 lakhs turnover business: State License FORM B.
- More than 20 lakhs turnover business: Central License FORM B.

Currently, 380 food articles come under 16 subcategories of SFP, in which traditional food products do not need approval. The imported standardized food needs FSSAI license to import, sale, and distribution. But the new product will be considered as non-standardized food article and need to get approval under Section 23.22 of the FSS Act, 2006. Imported food products need to follow Food Safety and Standards (Food Product Standards and Food Additives) Regulation, 2011, in which food product label must have the details of ingredients, additives, local importer contact detail, batch/lot/code number, and FSSAI license number. The regulation and acts are modified from time to time in India. Recent change in FSS Act was done in the year 2015, and nutraceuticals, health supplements, and functional and novel foods are proposed to put in Section 23.22 of FSS Act.

Although India is having a legal framework to regulate the food safety, it still faces issues in the implementation of safety standards and norms. The major reasons are: low number of food analysis laboratories, insufficient food analyst or techniques, and low performance of state laboratories. To overcome these limitations, Ministry of Food Processing started few programs like for "*Setting Up/Upgradation of Quality Control/Food Testing Laboratory*" to assist in laboratories infrastructure setup and upgradation. Effective collaborations between central, state, and private sectors can also help in solving the problems in food safety analysis. FSSAI has also started toll-free numbers 1800112100 and one online platform "*Food Safety voice*" to help consumers in their complaints and feedbacks regarding adulterated, unsafe, substandard food, wrong labeling, and misleading advertisements of various food products.

23.6 Conclusion and Future Perspective of Biosensors in Food Safety

Food safety and quality management are undoubtedly the major concerns at the global level that we need to confront and fight for without giving a break. In this chapter, we have explained the prominent role of biosensors in the detection of microorganism, pesticides, toxins, and other harmful chemicals in eatable food. We have also given the examples of nanobiosensors in food safety, although this is still at the nascent phase and needs improvement for a better and healthy future. We are basically aiming to stimulate the broader interest in developing the more sensitive, less time-consuming, and cost-effective biosensors, and their application in food safety. We hope to establish a bridge to fill the gap among food science, electronics, and nanotechnology that endeavors the effective collaboration in the interdisciplinary field and more novel biosensors will be designed and new ideas will spring up.

From the past few decades, biosensors have shown up-front advancement in almost every field of science, food technology, military, and health care. It has received heightened interest due to its lower detection limit in no time at low cost. However, this chapter focused on the use of biosensors in food quality management, but more research and new tool invention need to take care in this area.

Despite substantial progress, biosensors for food safety analysis have the following limitations: (1) Piezoelectric biosensors are difficult to use in microfluidic system as sample crystal oscillates. (2) Immobilization method can reduce the activity of transducers to enhance the signal. (3) Sample preparation and food complexities are uttermost challenges among all detection system. Their commercialization is still impeded by major following drawbacks (Hasan et al. 2014): (1) Complex and expensive components are used to design the biosensors to achieve high sensitivity and accuracy in the competitive market. (2) The stability of the biosensors is not maintained by in real samples analysis. (3) Low quantity of hybrid bio-elements is designed due to its higher complex method and high-cost value.

To overcome these limitations, the nanobiosensors may have played an important role due to its mediate small size, high sensitivity, low detection limit, and current flow. It has been not only in used to portable biosensor design, but it is also in use in smart packaging in eatable food and vegetables. It is still at an early stage, but it will bring enormous possibilities in this field. Recently nanotechnology-based quartz crystal microbalance (QCM) sensors, radio frequency identification (RFID) tags, and cantilever sensors are in use in research. QCM was reported to detect ethanol, citrinin toxin, and FBD microorganisms in eatable food products (Wang and Duncan 2017). These nanobiosensors are in use from manufacturing to packaging and storage of eatable food. Instead of the advancement in nanobiosensors for food safety management, nanomaterials might have a toxic effect and unforeseen risks to disturb food quality and ultimately affect the human health. There are some following limitations in nanobiosensors: (1) complicated procedure and costly reagents. (2) Other than QD or gold or carbon, there are limited nanomaterials used in commercially available nanobiosensors. (3) Due to the lack of recognition biomolecules, not all nanobiosensors can detect all food contaminations. (4) Small size of nanomaterials can increase the risk of bioaccumulation in body organs or tissues via food (5) Portable nanobiosensors could be a more convenient and effective method in real time on spot food sample analysis, but it is not pocket friendly. (6) No specific regulations in the production and use of nanomaterials in food and environment safety can also cause risk to the human health. (7) Public perception toward nanotechnology application in food safety also needs to improve. Lots of other factors like storage condition of food, their pH, growth status of microorganisms, and mode of food spoilage also affect the working of biosensors. These aspects should be concerned for future researches in designing the biosensors in food quality management.

Instead of having several challenges, biosensors have tried to prove their importance in maximally to benefit in order to maintain food quality and meet consumers demands of safe and healthy food. Recently, nuclear magnetic resonance (NMR), giant magnetoresistance (GMR), localized surface plasmon resonance (SPR), nanoparticle-assisted colorimetry, QD, CNT, and nanowires-based biosensors are in trend to ensure food safety (Krishna et al. 2018). Aptamer and smartphone-based biosensors are also at their infant stage in food safety area. QCM- and SPR-based label-free and real-time sensors are designed using DNA, aptamers/molecular imprinted polymers (MIP) to detect biochemical changes in food products. The qualities of QD, photostability, fluorescence spectra, full wavelength absorbance, and controlled fluorescence emission make it unique and sensitive in the food industry. Several biosensors are commercially available in the market to detect the biochemical reaction in spoilt food. OxyDot® detects the dissolved oxygen on the basis of fluorescence intensity and quenching of the metallic-organic fluorescent dye in food and drink products. SMART DOTS and RipeSense® detect the CO_2 and temperature changes; Timestrip Plus®, Timestrip Complete, and 3M MonitorMark are time-temperature indicators (TTI) to detect a change in temperature-dependent food; ToxinGuard detects the presence of pathogen and toxin in the eatable food (Srivastava et al. 2017). With the advancement in these sensors in food quality management, several researches focused on smartphone-based biosensor in food. Su et al. (2017) have designed smartphone-based system using cell viability biosensor to detect neurotoxin, okadaic acid, in seafood. Several other smartphone-based biosensors were designed to detect ALP as an indicator of incorrect milk pasteurization, OA and STX in shellfish, *V. parahaemolyticus* in fish samples, and *E. coli* O157:H7 and *S. enterica* in food samples (Rateni et al. 2017). Several other nanobarcodes, electronic nose, and electric tongue are recently designed for food safety management.

Moreover, the major concern in this whole idea is to control the potential toxicity of nanomaterials or other chemicals used in biosensor design in food safety as well as rapid, cost-effective, and more sensitive approach. These need to be taken care of in future work. New platform should also be designed for food quality assessment without extra step of sample preparation. In the future, sensing platforms can incorporate with sample extraction and separation units to improve the feasibility and portability of the food biosensors in field use. The long-term storage of enzyme and immunosensor-based biosensors are another challenge in safe food management. Minimizing background signals and false-positive results are needed to be achieved for higher specificity. Future food biosensors should also have the properties of multidetection, miniaturization, and automation along with low cost. Inter-laboratories studies for validating and testing the relevant biosensors for different samples with different number of samples should be performed to demonstrate the robustness and achieve regulatory approval for commercialization of the devices. Using smartphones or online systems along with cybersensors is still in early stage and constitutes a fertile area for future investigation. The safe and healthy food can be continuously monitored and maintained with the collaborative efforts of interdisciplinary scientists, academicians, and government.

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Chapter 24

Liposomes for Nanodelivery Systems in Food Products

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Abstract Nanotechnology has the prospective to offer novel solutions in the agriculture and food sectors. Food nanotechnology is increasingly gaining attention owing to opportunity of further improvements in development of novel and innovative and healthy foods. Nano-structured materials find promising applications in encapsulation of elements in the food and packaging thereof. Polymeric nanoparticles, liposomes, microemulsions, and nanoemulsions are among the nano-structured systems that have embraced the food sector. These materials have a great potential to elevate bio-accessibility, increase dissolving capacity, assisting commendable release, and safeguard food ingredients throughout the process from production to storage. In this chapter, the applications of nanoliposomes for their encapsulation and controlled release of food materials with enhancing the bioavailability are discussed. Additionally, their role as nanodelivery system for nutrients, nutraceuticals, enzymes, and food antimicrobials has been reviewed. Further, an outlook on the recent applications and their prospects in food technology and science has been emphasized.

Keywords Liposomes · Nanoliposome · Functional foods · Encapsulation · Bio-accessibility · Controlled release

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24.1 Introduction

Nanotechnology has emerged as multifunctional discipline comprising varieties of promising applications in various sectors. In food science and technology, various nanocarriers have been developed by utilizing tools of nanotechnology. Liposomes possess superior qualities of nanocarriers in food products. Liposomes are globular structures having 20 nm to certain microns, which are constructed through assembling phospholipids molecules. An aqueous core is formed by enclosing several phospholipid bilayers. A vesicular lipid bilayer structure—*nanoliposome*, is an emerging technology which includes encapsulation and safe delivery of biologically active ingredients. A "*nanoliposome*" possesses enhanced morphological, thermodynamic, and physical properties as nanometric version of a liposome. These nano-sized liposomes contribute toward providing large surface area for contact with the biological tissues and therefore, amplifying the bio adsorption of encapsulated components (Liu et al. 2015; Singh et al. 2012). Moreover, during the formation process, the lipid bilayer entraps a hydrophobic bioactive component. This entrapped compound then further released by diffusion through the membranes, or through the disruption of membrane due to change in pH or temperature (Thompson et al. 2009).

The applications of liposomes in food products have been studied in detail. Many reports have suggested that by considering the applications of liposomes due to its bio presence and biostability, they can be the best candidates for food ingredients delivery. Since liposomes possess very small size, they can be easily passed in the blood without any interference by other molecules and their inhibitory actions. They can be easily overlooked by biosystem and can maintain bioavailability. Liposomes can protect encapsulated food ingredients from various environmental factors including gases and humidity; from digestive tract juices; and enzymes and gut microbiota. Furthermore, in addition to the above advantages, liposomes being the phospholipid molecules also provide several health benefits to the humans. Phospholipids are integral part of the plasma membrane and contribute toward internalization and transport of various cellular particles by protecting them from deleterious external substances. The phospholipid bilayer possesses protein channels, facilitating adsorption of required molecules and removing waste components out of the cells. There are the reports suggesting that the role of phospholipids (especially phosphatidyl choline), to diminish cholesterol and triglycerides contents and thereby improving blood circulation through minimizing aggregation of blood platelets. Considering the air tight morphology of phospholipids, they can be smoothly ingested and digested without adding any buffers, flavors, fillers, binding partner or any coloration (Acosta 2009; Basnet et al. 2012; Keller 2001; Takahashi et al. 2009; Yang et al. 2013). Therefore, being the compounds of phospholipids, liposomes are widely used in food and diet supplements, therapeutic agents, bio carriers, and in nutrition. Figure 24.1 depicts the applications of liposomes in various fields.

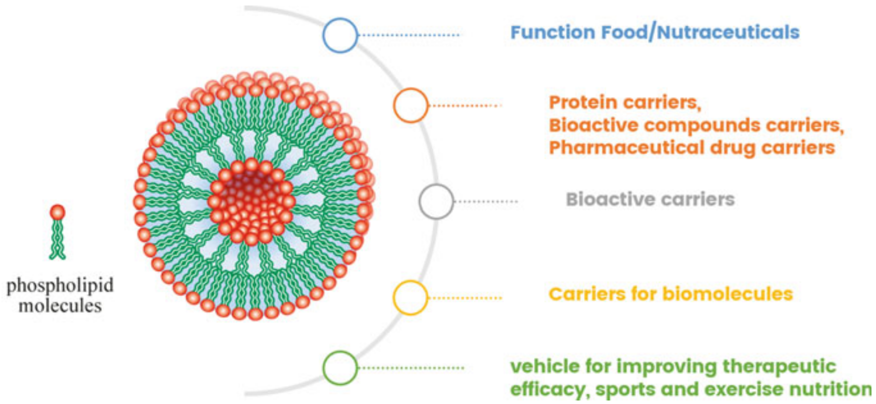

Fig. 24.1 Applications of liposomes in various products including food, pharmaceutical supplements, and as carrier molecules

24.2 Liposomal Encapsulation of Functional Foods/Nutraceuticals

The twentieth century has witnessed the development of functional foods viz. foods with added nutrients for the protection of human health and well-being. One major attribution of utilizing liposomes in food products is their ability to protect through encapsulation. Recently in the functional foods and nutraceutical industries, antioxidants are gaining increased attention owing to their free radical scavenging attributes. The encapsulation of antioxidants by liposomes can retain their activity besides improving their bioavailability and shelf life.

Encapsulation refers to protecting any nano- or micro-sized component from getting damage or involve in any undesired interactions. Also, encapsulation can be referred to packing any nano- or micro-structured component in the form of solid, liquid or gas for controlled and/or targeted delivery to the specific site at certain conditions (Dziezak 1988). The substances which are protected or the coated material is called as core substances or fill substances, payload, internal phase substances or actives. The material that protects or the internal phase is called as carrier materials, capsule, shell, membrane, or wall membrane (Gibbs et al. 1999). The nanocapsules provide protection to food compounds which are more sensitive, ensures minimal loss of nutrients, utilizes sensitive ingredients, facilitates time-based formulation, masks and preserves aromas and supplements, and converts liquids to solid components which can be easily controlled (Dziezak 1988; Gouin 2004).

Advancements in nanotechnology have enabled bioactive carriers to be custom made for specific bioactive agents to be targeted in the required sites and to be released in time-controlled manner. The nanocarriers provide good surface area, increase the bioavailability and enhance the solubility, enable time-controlled release of the actives to the specified target sites with greatest accuracy and precision. Due to nanoencapsulation, the amount of bioactives required is much less when compared to un-encapsulated actives (Mozafari 2006). As a result of encapsulation and regulated delivery of the active compounds, the effectiveness is improved, the applications range is widened, and the optimal dosage is ensured along with cost-effectiveness. By using nanoliposomes as nanocarriers, the reactive or otherwise sensitive core material is transformed into stable ingredients.

24.3 Liposomes as Protein Carriers

The encapsulation of proteins has been successfully carried out by liposomes. These encapsulated proteins still mains its physiological function under external environmental conditions. Furthermore, the internal layer of the bilayer functions as an organic solvent and the process is known as an adsolubilization. It is performed for lipid compounds to encapsulate at internal side of the bilayer. In one study, in order to enhance shelf life, two dairy products—a bacteriostatic glycoprotein called lactoferrin, and an antimicrobial polypeptide called nisin Z—were encapsulated by liposomes (Taylor et al. 2005). In another study, the nisin Z was encapsulated in liposomes made with marine lecithin (ML) or soy lecithin (SL), and it was found that a blend of free and encapsulated antibacterial compound was effective against a food pathogen—*Listeria monocytogenes* (Imran et al. 2015). The phospholipids are widely emerged as oral deliveries to enhance homogenization (Gaysinsky et al. 2005). The encapsulation by liposomes also provides antimicrobial activity of encapsulated ingredients which was reported by Gaysinsky et al. (2005). In ground pork and many dairy substances, the lipid oxidation was carried out by phosvitin which was entrapped by liposome. Also, many active ingredients activity was preserved for substantially long period. For instance, the 50% activity was retained by encapsulated vitamin C kept for 50 days in refrigerator, while the free ascorbic acid retained its activity only for 19 days (Wilson and Shah 2007). It is well known that the essential oil from the clove has antimicrobial effects by damaging the cell membranes. In one study, clove oil was liposome-encapsulated and evaluated for its antibacterial role against *Staphylococcus aureus* in tofu. The results have shown that pore-forming toxins (PFTs) secreted from *S. aureus* activated the release of clove oil from liposome, and the formulation successfully achieved inhibition of bacterial growth in tofu (Cui et al. 2015).

24.4 Liposomes as Bioactive Carriers

There have been reports suggesting the application of liposomes as bioactive carriers. Certain pigments including quercetin, anthocyanin, and other flavonoids such as lutein and vitamins were studied (Marsanasco et al. 2011; Toniazzo et al.

2017; Zhao et al. 2017). Once the compounds are encapsulated and exhibit improved behavior, these compounds are further named based upon their original forms. For example, ethosomes (ethanol-based), niosomes (nonionic surfactant-based), transferosomes (vesicular delivery), bilosomes (bile-based), and phytosomes (lecithin-based) are an improved form of liposomal encapsulated compounds. Since they act as vesicular carriers, they have not been studied in detail for food applications (Aditya et al. 2017). Niosomes provide potential alternative of vesicular carrier as liposomal encapsulation of hydrophilic compounds is achieved (Sharma et al. 2015). Phytosomes—a complex of natural compounds—are potential food-based delivery vehicle, improving potency and solubility of polyphenols. These characteristics facilitate their applications in various food systems (Ghanbarzadeh et al. 2016; Karimi et al. 2015). On the other hand, bilosomes are transformed niosomes.

24.5 Liposomes as Pharmaceutical Drug Carriers

According to pharmacological definitions, bioavailability is the fraction of a drug/bioactive which perfuses the circulation when introduced into the body and so can have an active effect (Andrew and Shargel 2015). As far as nutritional sciences are concerned, these substances cannot be defined under the scope of pharmacological definition. The utilization and absorption are representative of physiological function and nutritional status which differs greatly from one individual to another. Thus, in dietary supplements, the bioavailability is defined as the amount of the administered materials which is capable of being absorbed, used, and can be kept for storage (Srinivasan 2001). The drug delivery carriers must be structured in such a way that the bioavailability of the drug that is loaded inside is at maximum. Nanoliposomes are one of the emerging drug delivery systems which offer maximum bioavailability for the active ingredients. It is also important to consider the stability of the liposomes when it loaded with the actives. The nanoliposomes must possess good resistance against oxidation, as the oxidation processes tend to de-structure the bi-lipid layer of the liposomes causing the wastage of loaded active ingredients. If the nanoliposomes are designed with good antioxidant properties, it can withstand oxidation reaction that could happen in the mid-way before reaching the site of action.

24.6 Liposomes as Carriers for Other Biomolecules

There are a few biomolecules that include vitamins, minerals, and other trace elements which are also sometimes addressed as micro nutrition and/or essential nutrition. These kinds of biomolecules are to be taken externally through food as they cannot be synthesized within the body. Because of the low absorption rates of these biomolecules, normal dosage of these nutrients fails to reach the target sites or else less than the expected dosage reaches the target site. As a result of this, excess amount of the vitamins, trace elements, and other biomolecules/nutrients are administered to the recipient in order to match up the requirement. For instance, despite having distinct medicinal advantages and because of certain physiological functions including the insufficient absorption, profound hepatic, and intestinal metabolism and faster clearance outside the body, the curcumin exhibits compromised bioavailability (Kakkar et al. 2011). Further, the insufficient bioavailability of curcumin is considered as main hinderance for substantial uses in humans (Dulbecco and Savarino 2013). Administering the extra quantity of the nutrients can also cause negative effects in some cases, and to bypass this difficulty if the liposomes are loaded with these biomolecules, it can directly deliver the nutrients to the target sites.

In the food systems, most vitamins are unstable. The parameters including light, humidity, pH, temperature, and oxygen are critical for stability of compounds. Furthermore, the structure of vitamins, processing and their packaging have a crucial influence in their activity (Ball 2013; Singh and Das 1998). Vitamin C [ascorbic acid] and β-carotene are highly unstable, and can rapidly be oxidized by change in humidity and temperature. The oxygen content and heavy metals content during the storage and processing are key factors for maintaining their stability (Shade 2016; Yang et al. 2012). Studies have proved that vitamin E [α-tocopherol] loses its activity when subjected to harsh environment including change in oxygen content, temperature, pH (Khayata et al. 2012; Qian et al. 2013). Therefore, extensive studies have been carried out to preserve the activity of vitamins in food systems. The accumulation of vitamin A (retinoids) forming liposomal vesicles has been evaluated. It has been observed that under certain environmental conditions such as light, temperature, pH, and by adding cholesterol, the stability was improved. Liposome encapsulation and/or polymeric nanoparticles have been exhaustively investigated. It has been shown that liposomal entrapment significantly shelters the activity of several vitamins characterized by their solubility in water and fat (Emami et al. 2016; Fathi et al. 2012; Khayata et al. 2012; Qian et al. 2013; Shin et al. 2012; Tamjidi et al. 2013).

24.7 Liposomes as Vehicle for Improving Therapeutic Efficacy, Sports, and Exercise Nutrition

Due to health benefits, the ingredients supplements have huge potential for commercialization. The quality of ingredients, their formula, and benefits upon treatment are of primary considerations. However, the adsorption efficacy, routes of ingredients administration, and bioavailability of supplements are equally important. The efficacy of a supplement depends on biodegradability after targeted absorption and thereby, utilization within the tissues. Furthermore, one's health condition at the time of administration is a major factor which signifies body's capacity to take and then use it. Although certain digestive conditions including production of imbalanced stomach acids can block the breaking down of nutrients and adsorption thereof, these factors need to be considered in order to check the effect of a nutrient's bioavailability. The microflora of the intestines, the interactions with drugs, modified food habits causing compromised intestinal homeostasis, change in metabolism, solubility in water, and subsidiary compound used in coating the ingredients cause substantial effects on absorption. During the condition of poor health, few supplements are unrecognized by digestive system and therefore, accumulated as they are not dissolved in the intestine, resulting in assimilation of tablets and capsules causing many problems. In order to overcome these problems and thereby improving therapeutic efficacy, distinct delivery systems are developed. Past reviews have highlighted the emerging role of nanoliposomes as potent drug delivery systems (Abirami et al. 2014; Dev et al. 2012; Grobmyer et al. 2011; Wani et al. 2015).

Phyto-bioactive substances are secondary metabolites possessing increased health benefits usually present in highly low amount in different parts from seeds and roots to nuts, leaves, and their fruits. Examples include polyphenols, flavonoids, and triterpenoids that act as strong antioxidants (Hong et al. 2015; Kumari et al. 2012; More et al. 2013; Shah et al. 2015). Many herbal-based anticancer drugs including thymoquinone, curcumin, vincristine, quercitine, paclitaxel, shikonin, artemisinin, cinnamaldehyde, docetaxel, camptothecin, and oridonin have been widely used to target breast cancer (Heaney 2001). Various nanocarriers such as liposomes and micelles were used to combine these anticancer drugs to further amplifying anticancer activity. Recently, liposomal encapsulation technology (LET) an advanced method for nutrient delivery is developed to overcome problems associated with supplement industry. This technology has been previously used successfully pharmaceutical research to deliver various components including drugs, dyes, and therapeutic compounds to the targeted tissue in the body. Under this technology, many nutrients such as a vitamin C, which are normally less absorptive in nature, can be delivered in excess of ten times in the gut caused by high bioavailability; once carried with liposome, resulting in providing greater advantages (Yang et al. 2013).

Some compounds are slowly degradable and therefore descended their nutritional efficacy. This is one of the major challenges in producing fortified or enriched foods. In order to improve their stability, diversified nanoencapsulation methodologies are being used. Owing the beneficial characters, recently the food industry has adopted “Liposomal technology,” which was firstly utilized in pharmaceutical sciences. Enormous nutritional compounds including various enzymes, varieties of essential oils, different amino acids, antioxidants, vitamins, and distinct minerals have been encapsulated by nanoliposomes via liposomal technology (Mozafari et al. 2008). Recently, a study was conducted on liposomal vitamin C and their relevance to ischemia-reperfusion injury (Davis et al. 2016). In this work, the un-encapsulated, liposomal encapsulated, placebo with 4 g of vitamin C, and intravenous delivery were given separately. Among the four different routes of administration vitamin C, the liposomal vitamin C exhibited relatively higher level of vitamin C in the bloodstream than those given by un-encapsulated vitamin C. However, the intravenous vitamin C administration was still retained highest circulatory vitamin C. Considering various routes of vitamin C administration, the ischemia-reperfusion injury was protected by all the treatment methodologies except those given by placebo approach (Davis et al. 2016).

In order to evaluate the liposome-coated iron to revamp anemia in non-dialysis chronic kidney disease (ND-CKD) patients, Pisani et al. evaluated the samples after treatment. Though there were no significant differences between the performance of liposomal iron and intravenous iron supplement in the form of iron gluconate; the participants who had suffered at least one drug-related adverse event during the treatment was significantly lower in liposomal iron. However, a further intensive evaluation needs to be carried out to understand the performance of liposomal encapsulated iron and for possible incorporation in sports nutrition (Pisani et al. 2014).

Moreover, the potential benefit of liposomal vitamin C supplementation than that of oral vitamin C needs to be evaluated in detail which will further provide our understanding on the importance of these supplements after encapsulation if can be taken during exercises (Johnston et al. 2006). Although, there has not been any substantial research on implementation of liposomal technology which can be applied to sport nutrition. However, liposomal vitamin C can be a better alternative for improving exercise performances as the thorough studies on their potential effects could be investigated.

Some other liposomal encapsulation of supplementation must be considered also for sports nutrition. For instance, phenols exhibit lesser bioavailability however the antioxidant ability along with their anti-inflammatory behavior are a few important characteristics which need to be demonstrated for improving sport-based exercise performance. Aerobic capacity is one major aspect for improving exercise performances which has been reported to have positive effects by certain compound including quercetin, catechins, and resveratrol (Kressler et al. 2011; Nieman et al. 2010; Ota et al. 2016). It has also been reported that curcumin is advantageous for preventing muscle damage (Sahin et al. 2016). Liposomal phenols have already been used in treatment of cancer, like liposomal catechins and resveratrol can diminish the effects of cancer cells (Fang et al. 2006; Shindikar et al. 2016). There have been reports that liposomal resveratrol in combination with quercetin can enhance the effective treatment against pre-cancerous/cancerous skin lesions (Caddeo et al. 2016). Also, the liposomal curcumin in combination with resveratrol can potentially inhibit cancer (Shindikar et al. 2016). Thus, the previous reports exhibiting beneficial aspects of phenols could expand the scope of liposomal formulations in the context of exercises and sports. Table 24.1 describes various types of liposomal applications used in various compounds.

Table 24.1 Distinct applications of liposomes in various compounds

S. no.	Applications	Examples	References
1.	Functional foods/ nutraceuticals	Nanoencapsulation of functional food materials	Mozafari (2006)
2.	Protein carriers	Nisin Z and lactoferrin	Taylor et al. (2005)
3.	Bioactive carriers	Ethosomes, transferosomes, and phytosomes	Aditya et al. (2017), Ghanbarzadeh et al. (2016), Karimi et al. (2015)
4.	Pharmaceutical drug carriers	Dietary supplements	Srinivasan (2001)
5.	Carriers for biomolecules	Vitamin C [ascorbic acid] and β-carotene Vitamin E [α-tocopherol]	Shade (2016), Yang et al. (2012), Khayata et al. (2012), Qian et al. (2013)
6.	Vehicle for improving therapeutic efficacy, sports, and exercise nutrition	Polyphenols and flavonoids	Hong et al. (2015), Kumari et al. (2012)

24.8 Challenges and Future Outlook

Nutritional industry is expanding by leaps and bounds, and it is anticipated that applications of liposomes will be grown over the next decade considering their enhanced biocompatibility and their capability to bind with hydrophobic and hydrophilic therapeutic compounds (Shukla et al. 2017). Studies are sparse with regard to the toxicity aspects involved in uses of nanoliposomes. Additionally, the stability of the active ingredients in food antimicrobials needs to be investigated in detail. Besides, the strategies need to be developed towards reducing the cost of the marketable techniques too.

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Chapter 25
Nanotechnology for Enhancing Sea Food Production and Its Application in Coastal Agriculture

Utkarsh Jain and Nidhi Chauhan

Abstract The nanotechnology has progressively influenced agricultural and biotechnological applications which directly connected to our day-to-day life. Their current use in improved aquaculture and seaweed cultivation is very restricted, as toxicity is major concern. Several researches have been reported in use of nanomaterials synthesis through green synthesis method by using seaweeds or other aquatic medium and tons of researches demonstrated toxic impact of nanocomposites in aquaculture. But none study concluded the positive effect of nanomaterials on seaweed production and their role in economic growth. In this chapter, we put classified seaweed, their artificial production, their economical importance, and applications along with type of nanomaterials used in amelioratory production of seaweeds under one umbrella. We have shortlisted few studies on the use of Ag-, Fe-, and Mg-based metallic and magnetic nanoparticles, biological and chemical polymeric nanomaterials, nanoscale zerovalent iron (nZVI)-based nanocomposites, and several other conjugated nanomaterials in improved production of several seaweeds, majorly, *Chlorella* sp., *Chlamydomonas* sp., and *Spirulina.* These nanomaterials not only improved seaweeds production, they also negate photoinhibition and remediate aquatic environment for further seaweed production. Still, additional considerations of nanomaterial toxicity and environmental risk factors must be taken care of. Future research needs to be focused on high aquatic yield at minimum cost and low-risk involvement for safe and improved food nutrients as well as environment. Therefore, this chapter has outlined the upcoming needs in anticipation that scientists will upgrade the nanotechnology associated application in safe use of nanomaterials in improved aquaculture all around the world.

Keywords Seaweed · Nanotechnology · Coastal agriculture · Seaweed culture · Nanoparticles

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25.1 Introduction

Seaweeds, also known as marine algae, or macroalgae, show a range of structural organizations, which include the unicellular forms, microscopic flagellates, and massive kelps. They do not bear the reproductive structures like seeds, and flower. Their mode of reproduction is asexual, by means of spores. They lack the true roots, stems, and leaves (Brownlee et al. 2012). The function of root, i.e., attachment to the substratum is fulfilled by holdfast. Leaf-like structures, which are termed as frond, serve the function of nutrient uptake from the seawater. They possess chlorophyll to accomplish the process of photosynthesis, in order to synthesize the vital biomolecules. Products obtained from the seaweed make them as a potential raw material for the industries. The cultivation and harvesting of seaweeds had not gained its full potential. Based on the pigments acquired by the microalgae, they can be classified in three groups: green, red and, brown (Redmond et al. 2014) that are described below (Fig. 25.1).

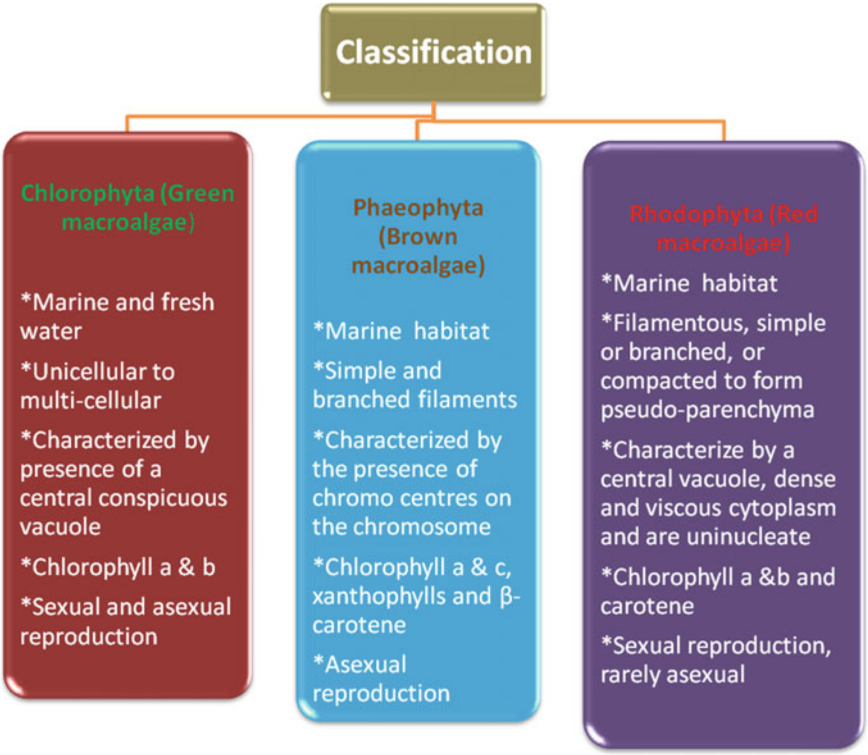

Fig. 25.1 Classification of seaweeds

25.2 Types of Seaweeds

25.2.1 Chlorophyta (Green Macroalgae)

Green algae reside in marine and freshwater. Their size varies from unicellular to multicellular forms. Their thalli vary in the calcification and can appear as a fan-shaped segment or feather-like or star-shaped. The thick cell wall is composed of cellulose and pectin. The protoplast is characterized by the presence of a central conspicuous vacuole, which is traversed by cytoplasmic strands. This class contains chlorophyll a and b and these pigments are stored in chromatophores. In chloroplasts, pyrenoid bodies are present. The obtained photosynthetic product from this group of algae is starch. Chlorophyta reproduce sexually by flagellated spores in isogamous, anisogamous, or oogamous mode. The asexual reproduction takes place with the help of non-flagellated spores, while vegetative reproduction occurs through fragmentation. Example of chlorophyta is *Ulvaceae* (Coppejans et al. 2009).

25.2.2 Phaeophyta (Brown Macroalgae)

Brown algae reside in marine habitats. They exhibit various forms like simple and branched filaments and highly branched ones. In this group, specialized sporangia are rare. The zoospores found in the group are naked and have a marked colorless beak at the end. This group contains two-layered cell wall, outer one is made up of alginate and shows mucilaginous appearance and inner one is made up of cellulose. The cells of these microalgae are uninucleate. This group is characterized by the presence of chromocenters on the chromosome. The cell organelles present in the microalgae include endoplasmic reticulum, Golgi bodies, vacuoles, fucosan vesicles, and chromatophores. Chromatophores found in this group change their movement according to the direction and intensity of illumination. Phaeophyta possess fucoxanthin, which is responsible for the varied coloration in leaves. Species like *Laminaria* have high amount of fucoxanthin, but species like *Fucus* have very low amount of the pigment. Other pigments possessed by phaeophyta are chlorophyll a and c, xanthophylls, and β-carotene. The obtained photosynthetic products from this group are laminarian and mannitol. Phaeophyta reproduce sexually through oogamy, isogamy, and anisogamy. Asexual reproduction occurs via zoospores formed in unilocular or plurilocular sporangia. Vegetative reproduction is carried out by fragmentation. Examples of phaeophyta are *Ecklonia maxima* and *Laminaria pallida* (Dharallear and Kavleekas 2004).

25.2.3 Rhodophyta (Red Macroalgae)

Rhodophyta reside in marine habitat ranging from intertidal to subtidal to deeper water. They show varied structural morphologies, as they can either live as epiphytes or as shells. Thallus of rhodophyta filamentous, simple or branched, or compacted, is to form pseudoparenchyma. The cell wall is two-layered: the outer layer is composed of mucopolysaccharide and the inner wall is made up of cellulose. Cells are characterized by a central vacuole, dense, and viscous cytoplasm and are uninucleate. The chloroplast varies its morphology from single axial to discoid forms. The pigments acquired by the group are phycoerythrin (red) and phycocyanin (blue). Other pigments possessed by rhodophyta are chlorophyll a and b and carotene. The obtained photosynthetic product from this group is Floridian starch. The sexual reproduction is quite complicated and involves fusion of spores from antheridium (male) and carpogonium (female). The asexual reproduction occurs rarely (Silva 2004).

25.3 Ecological Roles of Marine Macroalgae

25.3.1 Contribution to Primary Production

In coral reefs, primary production comes from algal turfs. Planktonic microalgae and algal symbionts also supply to reef productivity (Adey 1998). The macroalgae are taken up as food by herbivorous fishes, zooplankton, sea urchins, and crabs. Macroalgae also dispense the organic matter into the water and this is absorbed by bacteria followed by filter feeders. Large amount of organic matter is transported to other ecosystems like mangroves, seafloor, and seagrass meadows (Wild et al. 2004).

25.3.2 Nitrogen Fixation

Nitrogen being an essential component in the formation of biomolecules is absorbed by the plants. But the organic nitrogen is found in very low amounts in the ecosystem; hence, nitrogen fixation becomes very essential. In aquatic ecosystems, the function of nitrogen fixation is performed by blue-green algae, which is component of algal turf. These macroalgae have high growth rate but the fixed nitrogen is rapidly dispensed into the surrounding ecosystem (Larkum et al. 1988; Wilkinson and Sammarco 1983).

25.3.3 Construction of Coral Reefs

Macroalgae deposit calcium carbonate for providing the framework for the construction of reefs. The most important macroalgae performing the function of construction is crustose calcareous algae, as it attaches to the substratum and supplies a calcified barrier of tissues, in order to prevent erosion (Littler and Littler 1984). The calcium carbonate skeletons of Halimeda is another major contributor of reef formation, also it forms reef lagoons and white sand of beaches. Calcification acts as a defensive mechanism to prevent grazing, wave shock, to provide mechanical support and increased light-harvesting ability (Davies et al. 2004).

25.3.4 Bioerosion

The destruction of reefs is accomplished by endolithic algae, which reside in the skeleton of healthy and dead corals. These algae penetrate the calcium carbonate of the reefs and hasten the process of bioerosion in reefs, by physical and chemical processes. One such example is *Ostreobium*. This alga penetrates the calcium deposits and starts absorbing the calcium and accumulates it inside the cell. Endolithic algal communities furnish the energy demands of the ecosystem as well (Fork and Larkum 1989; Gektidis 1999).

25.4 Need for Seaweed Culture

Asia stands as the world leader in seaweed cultivation and more than 80% is contributed by China, Korea, and Japan. India has not taken up seaweed cultivation interestingly in the past though it is bestowed with a coastline of more than 17,000 km, embracing 821 species of seaweeds. Only recently, seaweed cultivation is picking up in certain coastal districts of the Tamil Nadu state. Natural seaweed stocks have become inadequate to meet the industrial requirements and hence cultivation of these important resources has become necessary. Considering the great demand for these resources in the international market and availability of adequate manpower and interest in the country, seaweed cultivation has a very good prospect and it can be developed as a successful cottage or cooperative sector industry (Mohamed 2015; Temkar et al. 2018).

The seaweed needs to be cultivated for:

- Restorative approach for fulfilling the nonavailability of ample quantity of seaweeds for various uses.
- Generation of occupation for the coastal people.
- Continuous availability of raw material for seaweed-based industry.

- Production of improved and uniform quality seaweeds for industrial use.
- Conservation of wild type seaweeds.
- Eco-friendly practice for the mass production.
- Sustainable pollution treatment strategy for coastal areas.

25.5 Techniques of Seaweed Culture

25.5.1 *Off-bottom (Post and Line)*

In this technique, a sequence of lines of 10 m length is spread between two posts made up of wood. This technique is utilized in lagoons, as the region is characterized by shallow water at low tide and is suitable for small-scale initiatives. The suspended lines are monitored continuously, and harvested each month, twice during tide periods. This technique is best suited for female workers as the harvesting can be done on foot. After harvesting of the seaweed, it is dried on land, prior to selling (Fig. 25.2).

25.5.2 *Longlines*

In this technique, a line of 50 m in length is used for the cultivation, which is anchored at the ends. The floats are also attached in the line after every 10 m, in

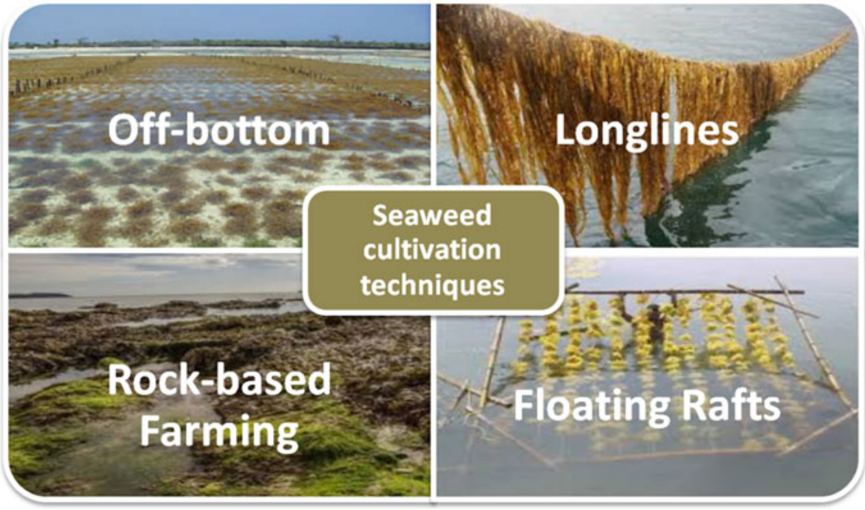

Fig. 25.2 Seaweeds cultivation techniques

order to provide support on the line. This technique is employed in relatively deep water of 4–10 m depth. To accomplish the task, farmers use boats to access the fields. Due to the use of boat, farmer can access the field at any time (Fig. 25.2).

25.5.3 Rock-Based Farming

In this technique, cuttings of the macroalgae are bounded to the rock with the help of an elastic band. After few weeks of growth, macroalgae develop the fixation points on its own. This technique can be carried out in low tide and on foot. The harvesting is done by cutting the new growth and leaving the older one for next cycle of growth. This technique is cost-effective and labor-saving. This technique is constrained by the factor of requirement of well-protected site from rough sea conditions (Fig. 25.2).

25.5.4 Floating Rafts

In this technique, a floating line is made and the macroalgae ropes are hung down from these lines. The ropes are weighted down using stones. This method offers an advantage of appropriate water movement but is limited to uneven growth. This technique is employed principally in protected bays in Asia (De San 2012) (Fig. 25.2).

25.6 Issues Related to Seaweed Farming

25.6.1 Ice–Ice Disease

This disease is caused by the stress conditions faced by seaweeds. This disease is characterized by degeneration of thalli, color transformation of thalli to pale white, and rotting of thalli. This disease causes a major problem of unavailability of cuttings for the subsequent production cycles.

25.6.2 Water Temperature

Seaweed growth is drastically hampered by the alteration in seawater temperatures. The ideal temperature of sea waterfalls in the range of 20–32 °C.

25.6.3 Prolonged Exposure of Seaweed to the Air

Air exposure to seaweed has a chronic effect on growth rates. This problem becomes more pronounced when the farmers take the new cuttings ex situ, i.e., after harvest, come to ashore site.

25.6.4 Salinity

Rapid drop in salinity becomes a limiting factor for the growth of seaweed. This rapid drop is a result of heavy rains in the catchment areas of river. The ideal salinity should fall in the range of 23–38 mg/l (ppm).

25.6.5 Algal Parasites

Epiphytic filamentous algae and other algal parasite can completely destruct the whole crop of seaweeds. This condition can be prevented by employing good monitoring of the farm, mobilization of technicians and farmers, attachments of small grafts, increased diversity of seaweed production sites, and modes of production.

25.6.6 Turbidity

Seaweeds are highly susceptible to the increased levels of turbidity caused by terrigenous material. This material sticks inside the thallus and induces ice–ice disease. Hence, it is advisable for the farmers to shake the lines at regular interval of time, in order to avoid the accumulation.

25.6.7 Storms and Cyclones

Seaweed farming is susceptible to bad weather. To overcome this disadvantage, the chosen field for production should be sheltered. In case of bad weather forecast, immediate mobilization of harvest and stock cuttings should be done.

25.6.8 Grazing of Seaweed

It is a seasonal problem faced by the seaweed cultivating farmers. The crop is grazed by herbivorous fish. The only possible remedy for the problem is to avoid the inhabiting areas of these fishes (De San 2012; Loureiro et al. 2015).

25.7 Nutritional Composition of Edible Seaweeds

The nutritional composition of *Bifurcaria bifurcata*, *Himanthalia elongata*, *Laminaria saccharina* (sweet kombu), *Gigartina pistillata,* and *Mastocarpus stellatus* was analyzed. The composition was found in following order: Ashes (24.9–36.4%), Protein content (10.9–25.7%), and lipids (0.3–0.9%). Protein content was found to be more in *Laminaria saccharina* in comparison to the other species. From the analysis, it was inferred that these species can be taken as a source of fiber, protein, and minerals, and are appropriate for human consumption (Gómez-Ordóñez et al. 2010). Edible forms of red (*Porphyra tenera*, *Chondrus crispus*) and brown (*Undaria pinnatifida*, *Laminaria digitata*, *Fucus vesiculosus*) seaweeds serve as a good source of essential minerals and trace elements (Rupérez 2002; Ruperez and Saura-Calixto 2001). *U. pinnatifida* and *H. elongata* increase the concentration of K, Ca, Mg, and Mn after addition to the food products. *P. umbilicalis* increases the concentration of serine, glycine, alanine, valine, tyrosine, phenylalanine, and arginine after addition to the food products. The edible seaweeds are good source of dietary fibers, proteins, and ash. Most abundant fatty acids found in the seaweeds are C16:0, C18:1ω9, C20:46, and C20:5ω3. Unsaturated fatty acids are found in brown seaweeds and saturated fatty acids are found in the red seaweeds (López-López et al. 2009).

25.8 Applications of Seaweeds

25.8.1 Seaweed as Foods

Red macroalgae (*G. tikvahiae*, *G. parvispora*, *G. coronopifolia,* and *G. salicornia*) are used as a source of food. Seaweeds provide high number of phytochemicals exhibiting antioxidant and antimicrobial properties. Presence of fibers and minerals helps in improving the mineral content and reduces the salt content. Addition of seaweeds to food commodities helps in decreasing their chemical preservative utilization. Seaweeds are rich source of polysaccharides, proteins, and polyunsaturated fatty acid (PUFA). The most abundant polysaccharide found in the brown seaweed is alginate. *U. pinnatifida* is a common ingredient in soup and salads (Gupta and Abu-Ghannam 2011; Paull and Chen 2008). It is also used as space food as 10 kGy Gamma irradiation can completely sterilize it and no subsequent deteoriation of the food takes place. This is rich in dietary fibers. Carrageenan provides improved effects on lipid oxidation, weight loss, and pH of the sausages. Carrageenan improves the microbiological and physicochemical characteristics of the low-fat fermented sausages (Koutsopoulos et al. 2008). *Ulva rigida* and *Lemna minor* were used for the preparation of bread. The shelf life was analyzed for these two breads against the controls. It was found that the bread prepared using *U. rigida* had a longer shelf life, in comparison to the controls. Similar result was found true for breads prepared by using *Lemna minor* (Pacheco-Ruíz et al. 2004).

25.8.2 Seaweed as Fermented Product

A study was carried out in order to analyze the growth of lactic acid bacteria on *Laminaria saccharina*, *L. digitata* and, *Himanthalia elongata*. The presence of growth showed the possibility of formation of fermented food products by using seaweeds. The seaweed having low-molecular-weight polysaccharides can be utilized as prebiotics. Seaweeds having alginate and agar as a component can be utilized as prebiotic (Gupta et al. 2011). *Clostrium acetobutylicum* ferments mannitol and laminarian found in brown macroalgae to butanol (Huesemann et al. 2012).

25.8.3 Seaweeds Used as Fertilizer

Seaweed can be utilized as biofertlizer for the development of sustainable organic agriculture (López-López et al. 2009). The high metal content found in seaweeds limits their application as biofertilizers.

25.8.4 Seaweeds in Medicine

Seaweeds are utilized as key ingredients in the traditional herbal medicines of Japan and China. These medicines are used for the treatment of rheumatism, influenza, worm infestations, tuberculosis, and cancer. Brown seaweeds are a rich source of terpenes. Terpenes display anticancer and antiviral properties. It is also utilized to treat malaria. Red algae are a rich source of tannins, which exhibit antibacterial properties (Nishizawa 2002).

25.8.5 Biomass for Fuel

Methane (biogas) can also be harnessed from seaweeds with the help of anaerobic digestion. Laminaria, gracilaria, sargassum and macrocystis were analyzed in their abilities in producing methane (Biogas). The gas yield for macrocystis was found to be high. The yield depends upon the level of alginate and mannitol content found in the seaweed. Mannitol concentration is critical for methane production. Gracilaria also produced a good yield of methane, but the yield is dependent upon carbohydrate content. Among these species, Sargassum shows least gas yield, and hence, cannot be utilized as good fuel (Bird and Benson 1987; Morand 1991).

25.8.6 Cosmetics

Seaweed extracts are utilized as ingredients in cosmetic products, like creams and lotions. The seaweed is utilized in cosmetic products due to the presence of carrageenan and alginate. Milled seaweed is utilized as a bathwater additive. Mineral-rich seaweed is employed in various therapies like massage hydrotherapy algae and marine mud treatments. Seaweeds are also utilized in rheumatic pain for pain relief. Paste mixtures of seaweeds are used in massage creams, in order to provide suppleness and to restore elasticity of the skin (De Roeck-Holtzhauer 1991).

25.8.7 Integrated Aquaculture

Cultivating two aquatic species together in a single compartment is termed as integrated aquaculture. The two species offer simultaneous benefits to each other. In similar way, cultivation of gracilaria was carried out with *Oreochromis mossambicus* and *Chanoschanos* fishes. This aquaculture benefits both fish and gracilaria. The waste material produced by fishes was utilized as fertilizer for the growth of gracilaria, and the epiphytes grow on the surface of gracilaria were taken as food materials for the fishes. Similar cultures of gracilaria were also been tested with shrimps in cage cultures. The culture analysis revealed that this kind of cage culture enhances the economic value of both seaweed and shrimp. Gracilaria cultivation is also attempted with salmon farms. It was observed that the seaweed growth was high, and the seaweed also eliminated the fish excreted ammonium (Neori et al. 2000; Troell et al. 1999).

25.8.8 Wastewater Treatment

(a) Treatment of wastewater to reduce nitrogen- and phosphorus-containing compounds

Seaweeds are utilized to eliminate the phosphorus and nitrogen content of the sewage effluents. Ammonium is the most common component of wastewater ejected from agriculture and household. Seaweeds take these ions as a source for nitrogen and utilize it as a metabolite for growth. Uptake of phosphorus is higher than the need for seaweeds. Monostroma and enteromorpha are tolerant toward the salinity of the water. Their use on a large-scale is yet to be implemented, although this may change with the increasing realization of the need to protect marine environments (Schramm 1991).

(b) Removal of toxic metals from industrial wastewater

Seaweeds are utilized as the biological indicator for the identification of pollution caused by heavy metals, as they accumulate these heavy metals. The seaweeds employed for this purpose are ecklonia, sargassum, laminaria, enteromorpha and, ulva. ecklonia, laminaria and macrocystis are utilized for the removal of cadmium, zinc, and copper ions from wastewater. A similar study was performed by using *Durvillaea potatorum*, *Lessonia flavicans*, and *Ecklonia maxima* to remove the metals like copper, nickel, lead, zinc, and cadmium ions from wastewater (Jin-Fen et al. 2000).

25.9 Role of Nanotechnology in Seaweed Production

After the increased demand for nutrients, resources in gradually increasing population, industries and farmers have increased their production. The nanotechnology has also played important role in increasing seafood production with using selenium, iron-like supplements in their environment. Appropriate nanomaterials increase bioavailability and stability of functional nutrient, avoid decomposition, show antimicrobial activity to protect product, and exhibit nanofiltration of water (Can et al. 2011). Recent years focused on seaweed-based biofuel production at minimal cost and obtain efficient product. The unique and physiochemical properties of nanomaterials remove all obstacles to achieve high yield and increase nutrient contents in seaweeds through following methods (Lee et al. 2015):

(a) Emphasize nutritional competition to increase intracellular lipid accumulation without killing cells.
(b) Light backscattering enhances cell growth in seaweeds.
(c) Repeated use of magnetic nanoparticles exhibited one-pot harvesting.

The seaweed cultivation and harvesting can be performed through direct and indirect methods. To avoid high nanomaterials concentration in water to hinder the light absorption by cells, few researchers used nanomaterial-modified bioreactor that results in high seaweed yield. Centrifugation, electrophoresis, filtration, and air flotation are the most common techniques for seaweed harvesting at large level (Lee et al. 2014c). These techniques exhibited low toxicity, recyclability, and improved harvest efficiency, though small size and low concentration of seaweeds completely depend upon seaweed environment, pH condition, and type of microalgal species (Yoo et al. 2014). Unfortunately, the conventional method of seaweed harvesting is difficult in biorefinement setting and their complete dependence on microalgal sp. affect harvesting efficiency. Therefore, nanomaterial-based techniques may overcome these limitations and positive result may be gained by researchers.

25.9.1 Magnetic Nanoparticles

Magnetic nanoparticle-based harvesting techniques are come into limelight, and pH sensitivity of Fe_3O_4 was reported in number of researches recently. Researchers exhibited significant harvesting efficiency (approximately 95%) of negative-zeta-potential microalgae such as *Botryococcus braunii, Chlorella ellipsoidea,* and *Nannochloropsis maritime* from fresh and marine water using nanosized Fe_3O_4 magnetic particles within 5 min (Hu et al. 2013; Xu et al. 2013). Hu and colleagues have also developed *C. ellipsoidea* harvesting system on rotating permanent magnet drum, but the system still needed improvement for further scale-up as harvesting efficiency decreased with increasing microalgal concentration and flow rate (Hu et al. 2014). In another study, oleaginous *Chlorella* sp. was harvested and reusability of Fe_3O_4 magnetic nanoparticles demonstrated. Lee and colleagues have reported high lipid content *Chlorella* sp. harvesting due to electrostatic interaction between microalgae and Fe_3O_4 magnetic nanoparticles at low pH, though the NP could have separated via increasing pH and reuse it in further harvesting (Lee et al. 2014a).

25.9.2 Polymer-Based Nanoparticles

After successful use of magnetic nanoparticles in seaweeds harvesting system, naturally occurring polymers were also demonstrated their significance in this field. Lee and colleagues reported aluminum and magnesium-based amino clay in conjugation with (3-Aminopropyl) triethoxysilane organo functional material for high harvesting efficiency in 30 min in natural pH for harvesting oleaginous *Chlorella* sp. from supernatant solution (Lee et al. 2013). However, Ca-APTES and magnesium-3-[2-(2-aminoethylamino) ethylamino] propyltrimethoxysilane (N3)-based amino clay exhibited low water solubility due to their large particle size distribution and delamination delay which results into low harvesting efficiency (Lee et al. 2013). The stable nZVI coated amino clay at 1.0 amino clay/nZVI ratio, was also reported to harvest almost 100% of the *Chlorella* sp. within 3 min (Lee et al. 2014b).

25.9.3 Hybrid Nanomaterials

Recently, researchers have focused on nanocomposites application in almost every field rather than using single nanoparticles. Negative charges on magnetic nanoparticles and microalgal system call for advancement in harvesting technique, and the different hybrid nanomaterials can be used to overcome this problem. In this direction, Lim and colleagues have demonstrated significant *Chlorella* sp. harvesting via polydiallyl dimethylammonium chloride (PDDA) coated rod-shaped ($\sim$98%) over spherical ($\sim$80%) Fe_3O_4 magnetic nanoparticles (Lim et al. 2012). Similarly, PDDA coated rod-shaped Fe_3O_4 magnetic nanoparticles efficiently harvested (90%) *Scenedesmus, Spirulina, Chlorella, Tetraedron, Haematococcus*, and *Dictyosphaerium* from fishpond within 3 min (Toh et al. 2012). They also run series of experiments to demonstrate reusability of above nanomaterial harvesting system on the basis of their ionic strength. In another study, Hu et al. (2014) explained 98% harvesting efficiency of polyethylenimine (PEI) coated Fe_3O_4 magnetic nanoparticles for *C. ellipsoidea* in 2 min based on langmuir adsorption isothermal model (Lee et al. 2014a). They also proposed electrostatic attraction and nanoscale interactions between the nanocomposites and microalgal cells as major for their separation.

25.9.4 Iron and Magnesium Nanoparticles

Several other researchers have focused direct use of photosynthetic iron and magnesium nanoparticles, in which iron also proved their importance in lipid accumulation in *C. vulgaris* (Liu et al. 2008). In another study, ethylenediaminetetraacetic acid (EDTA) chelated soluble iron and synthetic nanoscale zerovalent iron (nZVI) nanoparticles were studied for *Pavlova lutheri, Isochrysis galbana, and Tetraselmis suecica* production (Kadar et al. 2012). Similar growth rate was obtained in all three seaweeds in EDTA-based iron and nZVI, though high lipid accumulation was reported in *P. lutheri* and *T. suecica.* The high lipid contents were justified via exhibiting production of ROS and oxidative stress due to nZVI (Kadar et al. 2012), along with stress condition due to iron uptake competition among the cells (Zhang et al. 2013). Similarly, Sarma et al. (2014) demonstrated increased chlorophyll production results into photosynthesis in *C. vulgari* when $MgSO_4$ nanoparticles supplemented carbon source glycerol solution was used (Sarma et al. 2014). Though $MgSO_4$-based microalgal flocculation caused low penetrated light utilization, hence, to increase chlorophyll content to sustain overall photosynthesis. In summary, it followed adaptation mechanism. The direct use of silica nanoparticles also exhibited decreased cell growth in *Scenedesmus obliquus* (Wei et al. 2010) and cell increment in *C. vulgari* (San et al. 2014). They hypothesized that micronutrients of silica nanoparticles not only give positive effect on seaweeds, but also the cell growth controlled by particle size, dosage, and seaweed species.

25.9.5 Silver Nanoparticles

Torkamani and colleagues have demonstrated significant cell growth of *Chlamydomonas reinhardtii* and *Cyanothece 51142* after blue light backscattering from silver nanoparticle solution (Torkamani et al. 2010). In another study, spheroidal AgNPs and Au nanorods alone or in combinations were used near a photobioreactor which results into increased light uptake and chlorophyll and carotenoid accumulation (Eroglu et al. 2013). They also reported reuse of nanoparticles suspension without any toxicological and contaminations problems. Other then seaweed production and photoinhibition, stimulation of very specific seaweed synthesis can also be controlled by size and concentration of nanoparticles (Lee et al. 2015).

25.9.6 Complex Magnetic Nanoparticles

After achieving success in Fe_3O_4 NP-based harvesting system, researchers focused on other ferrites. Seo and colleagues have used chemically stable APTES decorated $BaFe_{12}O_{19}$ nanoparticles for harvesting oleaginous *Chlorella* sp. with harvesting efficiency of 98.6–99.5% in spite of having large particle size range 108–1.17 μm (Seo et al. 2014). They also reported enhancement in harvesting efficiency along with increment in nanoparticles size and detachment efficiency in aqueous solution of pH12.

25.9.7 Other Nanoparticles

Sibi and colleagues have demonstrated higher production of *C. vulgaris* after induced metal resistance against copper, zinc, lead, and magnesium-based nanoparticles (Sibi et al. 2014). They reported improved biomass, lipid accumulation, and cellular pigments in presence of metal salts after their habituation toward these nanoparticles. Several other researchers have focused on seaweeds-based biodiesel production and improved effect due to nanomaterials. Yu and colleagues have demonstrated improved flocculation efficiency which results into higher lipid production and ultimately high biodiesel production via use of cation modified cellulose nanofibrils (CNF) and cellulose nanocrystals (CNC) on *Chlamydomonas reinhardtii* strain cc-124 (Yu et al. 2016). Similarly, N-doped graphene nanosheets (NGS) reported to improve biomass and triacylglycerols (TAG) production from *Chlorella pyrenoidosa* in fresh water compare to N-doped carbon nanosheets (CNS) (Khanra et al. 2017).

25.10 Conclusion and Future Perspective

Although gradually increasing importance of nanomaterials in seaweeds cultivation and harvesting, the area is still at infancy and requires rooms for their practical implementation as well as adverse event reduction. Effect of different nanoparticles and their interaction with different seaweeds in variable environmental conditions requires precautionary measurement. The stability and costing of functionalized nanomaterials can be maintained with minimum dosages and high reactivity. Although, recovery and reuse of these effective nanomaterials have been a major concern in seaweed harvesting and production while controlling environmental pH and dosage toxicity. Therefore, magnetic nanoparticles can be very beneficial in terms of recycling and NM functionalization with biocompatible materials that may help in lower the toxicity. This may help in large-scale production of seaweeds at minimized cost in environment-friendly nature. Although magnetic nanoparticles reported increased dispersibility to achieve high harvesting capacity, their oxides were difficult in recycling or in reusability. Other than magnetic nanoparticles, cubic spinel ferrites conjugated Mn, Cu, Zn divalent ions reported high chemical stability, excellent biocompatibility, and low production cost (Lee et al. 2015; Solano et al. 2012), however, they also exhibited low stability against oxidation due to their higher magnetism (Borlido et al. 2013). This rise questions toward their use in seaweed harvesting system.

The efficiency and effectiveness of nanoparticles are basically depending upon microalgae species and their environmental conditions such as pH and temperature. Therefore, additional research on use of nanomaterials based on seaweeds and surrounding environment is strongly encouraged in order to achieve desired result. Several researches have been focused on physiochemical characteristics of nanoparticles and biological nature of microalgae to improve their production. Therefore, several models have also been developed for microalgae flocculation-based low-cost nanoparticles. The contact angle of probe liquids, surface potential, thermal energy, and gravitational pulling under low-magnetic field needs to be studied before these nanomaterials production. Several nanomaterials fabrication techniques such as solution-based methods, photolithographic, or microfluidic processes, upsurge the shape-based nanoparticles flocculation for seaweeds. In this direction, amino clay and chitosan have demonstrated excellent harvesting performance, but their preparation cost is high and that bottleneck to scaled-up process. Therefore, efficient and inexpensive nanomaterials synthesis should be primary concern for in economical microalgae harvesting process. In meantime, other promising harvesting techniques can be further analyzed for their effectiveness. Recent years have also focused on integrated techniques for effective nanomaterial synthesis and their use in simultaneous harvesting along with fruitful oil extraction process with using any solvent system.

In conclusion, seaweeds contribute environment and economic development, and their effective production need to be our first concern. Several reports on nanomaterials toxicity were reported which is much higher than their use in seaweed production (Source: Pubmed and Goole scholar. Keywords: nanomaterials, toxicity, seaweeds). Therefore, rational designs of nanomaterials should be predetermined and examined before their practical implementation. These designing models should have resulted into stable, efficient, cost-effective, and easy recycling of nanomaterials, along with practical implementation at large-scale and their commercialization in batter way.

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Chapter 26
Microfluidic Devices and Their Application in Modern Agriculture System

S. Vasantham, S. Nagabooshanam, Shikha Wadhwa and Ashish Mathur

Abstract Microfluidics involves processing or manipulation of minute fluid volumes from 10^{-9} to 10^{-18} litres using channels with dimensions of the order of 1–100 μm. The technological implications give this field importance where the purpose is to develop entire laboratory functionalities within a hand-held chip. Recently, owing to great interest in miniaturization, microfluidics is used in many scientific fields. The list of feasible applications and the developed systems in various scientific fields is very long. This chapter focuses on the application of microfluidics-based sensors in agriculture and food science. After a brief description of the basics in microfluidics, a special phenomenon associated with the microscale is introduced. Concurrent technologies in the field of agriculture are then discussed in detail; primarily concerning its application as sensors for food safety and security. Several constraints are elaborately examined wherein detection of toxins such as pathogens within the crop or food, pesticide concentration and other miscellaneous additives like heavy metals becomes vital.

Keywords Microfluidics · Agriculture · Miniaturization · Sensors

26.1 Introduction

Microfluidics is the art of both science and technology, where fluid motion is carefully studied within microchannels or micro-machined devices consisting of small-size chambers and tunnels through which the flow of the fluid is understood. Microfluidics, as the name suggests, comprise of fluid volumes ranging from 10^{-9} to 10^{-18} l flowing through microchannels with dimensions of a ten to several hundred micrometres (Whitesides 2006). The fluid behaviour in the micrometre scale is entirely unique and these unique features, consequently, lead to new sci-

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entific experiments and innovations (Brody et al. 1996). Simple scaling and shrinking of existing large devices do not bode well in the microscale, often disrupting their innate functionality and is counterproductive (Purcell 1977). Implementation of new designs or modifications to the existing ones must be made to fully utilize and exploit the different kinds of forces operating at the microscale.

To gain a better understanding of fluid flow within microchannels, one needs to understand the math behind why such a phenomenon occurs, specifically the Navier–Stokes (NS) equation which explains the flow of any fluid (Marsden and Chorin 1993). In principle, the NS equation can be over simplified to denote the Newton's second law which defines force as a product of the mass and acceleration of a body.

$$\rho\left[\frac{\delta V}{\delta t}+(V.\nabla)V\right]=-\nabla P+\rho g+\mu\nabla^2 V$$

In the above equation, ρ is the density of the fluid, g is the acceleration due to gravity, P is the pressure, μ is the viscosity and V velocity of the fluid. The right-hand side of the equation corresponds to the various forces, firstly, the pressure term where the flow of the fluid is influenced largely where there is a pressure gradient within the direction of flow. The ρg term accounts for the external forces acting on the fluid such as gravity, electromagnetic forces, etc. and finally, the last term on the right-hand side of the equation which constitutes the internal forces due to fluid–fluid collisions. A major component which dominates here is the viscosity of the fluid.

Effects such as flow of the fluid, be it laminar or turbulent, resistance to the flow by the fluid, diffusion, surface area-to-volume ratio and surface tension become dominant when studying fluid behaviour in the microscale. To define the flow system (laminar or turbulent) of a fluid flow, one must know Reynolds number (*Re*) which is expressed as,

$$Re=\frac{\rho v D_{\mathrm{h}}}{\mu}$$

where ρ is the fluid density, v is the characteristic velocity of the fluid, μ is the fluid viscosity and D_{h} is the hydraulic diameter. The hydraulic diameter is a computed value that depends on the channel's cross-sectional geometry (White and Corfield 2006). The Reynolds number, which is a dimensionless quantity, determines the turbulence of flow. It is extremely low at small scales, meaning that the fluid flow pretty much stays laminar. As the size of the channel in which a liquid flow becomes smaller and smaller, local effects such as surface tension, laminar versus turbulent flow, Reynolds number and surface chemistry tend to play a larger role in the physics and chemistry of the reactions under investigation. Since the dimension of the channels in the microscale is usually small, a Reynolds number value of less than 100 is expected, often less than 1.0. Laminar flow is more structured and ordered thereby helping the researcher predict and understand how molecular transport occurs through microfluidic channels.

26.1.1 Special Phenomena Associated with Microscale

26.1.1.1 Laminar Flow and Turbulent Flow

In laminar flow, the particle in a fluid stream flow smoothly in one-oriented direction and is not a random function of time (Fig. 26.1a). As the size of the microchannel is very small, the flow is nearly laminar always and the important force is viscous force. In case of turbulent flow, an unsteady flow where fluid particles move along irregular paths and inertial forces are the key players and viscous forces are negligible (Fig. 26.1b) (Ismagilov et al. 2000).

26.1.1.2 Diffusion

This is the process involving transportation of fluid particles from a region of higher concentration to lower concentration by random motion (Fig. 26.2). Diffusion is expressed by the following equation, in one dimension,

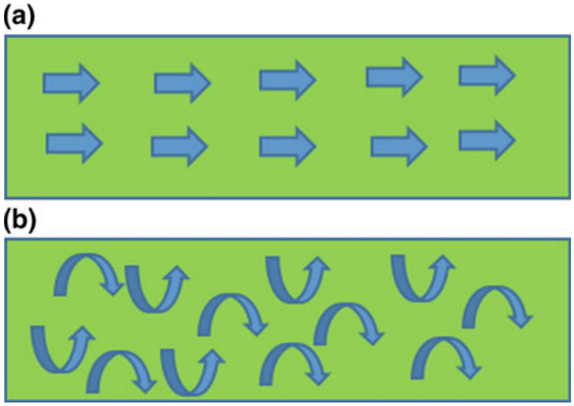


Fig. 26.1 **a** Laminar flow and **b** turbulent flow

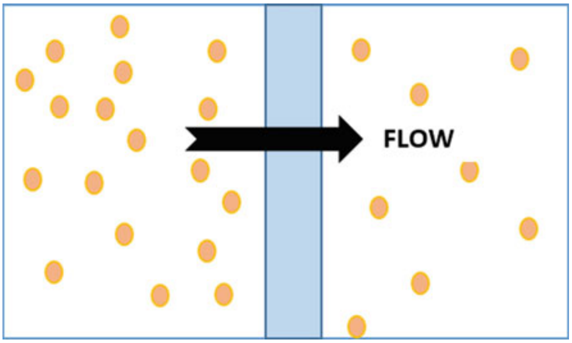


Fig. 26.2 Diffusion process from higher concentration gradient to lower concentration gradient

$$d^2 = 2Dt$$

where d is the distance in which a particle moves in a time t and D is the diffusion coefficient of the particle. At microscale, the diffusion plays vital role as the distance varies to the square power. At the microscale, these microchannels can create concentration gradients possessing complex profiles since the diffusion times are short at the microscale (Dertinger et al. 2001; Jeon et al. 2000). While coming to mixing schemes, one must maximize the interfaces between the fluids in order to allow the diffusion process to happen very rapidly. The advantage at microscale level is that the diffusion time is less as the distance between the microchannels are smaller (Jacobson et al. 1999; Liu et al. 2000).

26.1.1.3 Viscosity

Viscosity is basically the friction between molecules of the fluid in question. Viscosity determines the rate of flow of a fluid; for example, a fluid with a high viscosity tends to flow slowly as compared to one with a low viscosity which glides or slides faster. Higher the viscosity, more is the tendency of the fluid to resist motion or movement.

26.1.1.4 Capillary Phenomenon and Surface Energy

Capillary force is the force in which the liquid moves through the microcapillaries due to cohesion or surface tension (Fig. 26.3). Surface tension can be defined as a cohesion effect at the interface of liquid or gas between the liquid molecules. The tension on a liquid surface can be directly related to the measure of surface energy of that liquid. For example, the height up to which the water will travel through a capillary is directly related to the surface free energy of the water and inversely related to the radius of the capillary (Zhao et al. 2001).

26.2 Fabrication Techniques for Microfluidics

26.2.1 Photolithography

The fabrication process for producing microfluidic devices involves photolithography, where patterns representing microfluidic and electric features are transferred onto a photosensitive substrate via ultraviolet illumination using a chromium photomask. Then, the elements are revealed by chemical etching. Multi-layered structures are produced by the application of photolithography via successive photomasks. Photolithography has continuously improved not only in the ability to

Fig. 26.3 Illustration of capillary phenomenon

resolve ever-smaller features, but also in the production of high-aspect-ratio features. This is particularly important in the fabrication of microfluidic channels. Despite each of the photolithographic processes having its own specific requirements, a general approach of the photolithography technique involves photo-resist coating which is then masked, exposed and developed into the desired pattern required. There is a plethora of fabrication techniques based on the kind of pattern required, its resolution and the overall processes involved within the pattern transfer, which can be summarized in the following sections (Fig. 26.4).

26.2.2 Soft Lithography

Soft lithography is an alternative fabrication technique, based on direct printing or moulding of polymers (Galarreta et al. 2013). Instead of stiff photomasks, elastomers are used as stamps, moulds or masks, in soft lithography, to replicate the patterns. In soft lithography, the silicone elastomer polydimethylsiloxane (PDMS) is the preferred choice due of its ease of casting, its hydrophobicity, sealing

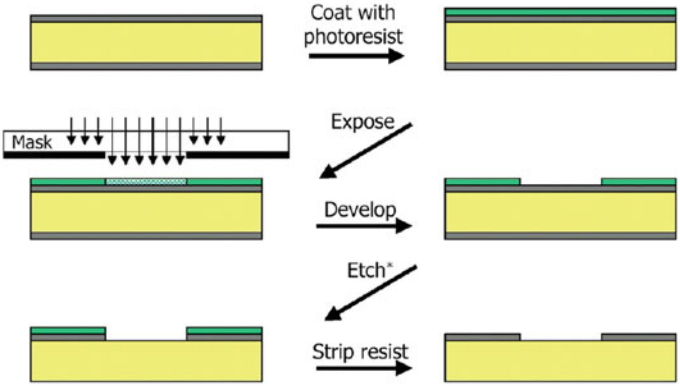


Fig. 26.4 Various processes involved in photolithography

properties and biocompatibility. Soft lithography is recommended only for rapid prototyping in research. Due to the soft materials used in soft lithography, stamps and moulds getting distorted are the problems that are preventing soft lithography from becoming a viable manufacturing technique (Table 26.1).

Table 26.1 Advantages and disadvantages of various fabrication techniques

Fabrication techniques	Advantages	Disadvantages	References
Hot embossing	Ideal method for bulk production Microstructures can be well replicated Precise in nature	Only thermoplastics can be embossed The entire process may take longer compared to other techniques Fabricating 3D structures is a herculean task	Fiorini and Chiu (2005)
Injection moulding	Automated process ideal for production in bulk with very fine features	Only thermoplastics can be used in this technique Mould cost is high Size precision is still an issue	Fiorini and Chiu (2005), Sollier et al. (2011)
Laser photoablation	Rapid process	Not all materials are process able with this technique Challenges include mass producibility and precision in size	Becker and Locascio (2002), Fiorini and Chiu (2005), Roberts et al. (1997)

(continued)

Table 26.1 (continued)

Fabrication techniques	Advantages	Disadvantages	References
Soft lithography	Cost-effective procedure with excellent control over size precision. 3D geometries with high resolution are possible	Vulnerable to deformation and defects Fabrication of circular geometries is cumbersome	Fiorini and Chiu (2005), Xia and Whitesides (1998)
X-ray lithography	High-resolution technique. Patterns are straight and smooth on the edges as well	Not feasible for most applications due to high cost Also, the technique requires a lot of time	Mappes et al. (2007), Romanato et al. (2004)
3-D printing	Rapid, low-cost technique	Mass production and size precision are difficult Cannot handle multiple fabrication sessions in succession	Wu and Gu (2011)

26.2.3 Laser Micromachining

Laser micromachining employs a variety of lasers ranging from CO_2 gas lasers to solid-state lasers. The CO_2 gas laser is a pulsed microsecond infrared laser operating between a wavelength range of 9.3 µm and 11 µm. A solid-state laser, on the other hand, is a femto-to-nanosecond pulsed laser operating at wavelengths of 266 nm and 1060 nm. A lot of factors play a crucial role in determining the kind of laser to be used for material processing and the application involved. When photons are strongly absorbed in a sub-micron depth onto the surface of the material, one can say that an optimal laser micromachining has been obtained. The mode of delivery of the photons determines the quality of the micromachining achieved. If the photons are delivered in a short-duration burst, they tend to create a minor explosion on the material surface facilitating the ejection of particulates either gaseous or solids from the irradiated site without causing significant thermal degradation (melting, sputter, recrystallization, etc.) in the surrounding region. Ultraviolet lasers are usually preferred for micromachining application over others since the absorption of shorter wavelengths by most materials is much stronger than longer wavelengths. The following table compiles a list of advantages and disadvantages of the various fabrication techniques employed (Rodrigues et al. 2015).

26.3 Lab-on-Chip Devices

A sensor is a device capable of detecting and responding to an incoming stimulus with a respective output that corresponds to the stimuli and has huge potential in various field of agriculture (Fig. 26.5). For example, a thermometer is a sensor which can detect a rise or fall in body temperature and produce a human-readable output in terms of a corresponding value. Thus, a sensor possesses the ability to convert a physical parameter such as temperature, pressure, force, velocity and humidity. into a human-readable signal such as a digital value by means of its measurement either electrically or optically or some sort of a sensing mechanism. Samples that need to be measured are collected and analysed with the help of a suitable sensor capable of producing a meaningful output. This sensor then transforms the output into electrical signals with the help of some electronic components which are then either displayed onto a display or outputted as an accurate digital value.

Lab-on-chip technologies are currently the norm due to their inherent ability to integrate several functions within a single device which is portable and capable of point-of-care testing (PoC), which would otherwise take an entire laboratory to perform all the tasks such as mixing, detection and analysis. Scheme 26.1 illustrates the different capabilities of LoC device. Microfluidics provides a subtle platform for the operation of LoC devices where manipulation of minute amounts of fluids along thin, narrow channels in the microscale is made possible (Fig. 26.5). LoC are hybrid devices which integrate electronic components with fluidic components on the same chip. LoC technology emphasizes on efficient sample detection and separation, minimal reagent consumption, integration, increased sensitivity, chip programmability and sterilization. LoC functionality encompasses handling of samples, filtering and mixing, as well as analysis and monitoring. A typical LoC device consists of microchannels, for the flow of liquid samples inside the chip. It may also integrate components such as micro-electrodes, thermal elements, microvalves, microfluidic mixers or optical apparatuses for measuring, sensing and actuating.

26.4 Application of Microfluidics in Agriculture System

The most commonly used techniques to detect and quantify various substances used in agriculture include, inductively coupled plasma mass spectroscopy (ICPMS) to perform an elemental analysis to check for the presence of heavy metals in food produce, atomic absorption/emission spectroscopy (AAS/AES) to measure trace quantities of elements accurately, high-performance liquid chromatography (HPLC), gas chromatography (GC), mass spectroscopy (MS), etc. These techniques demand a technically skilled individual for the operation of such instruments which are quite expensive to procure and involve wastage of plenty of chemical reagents

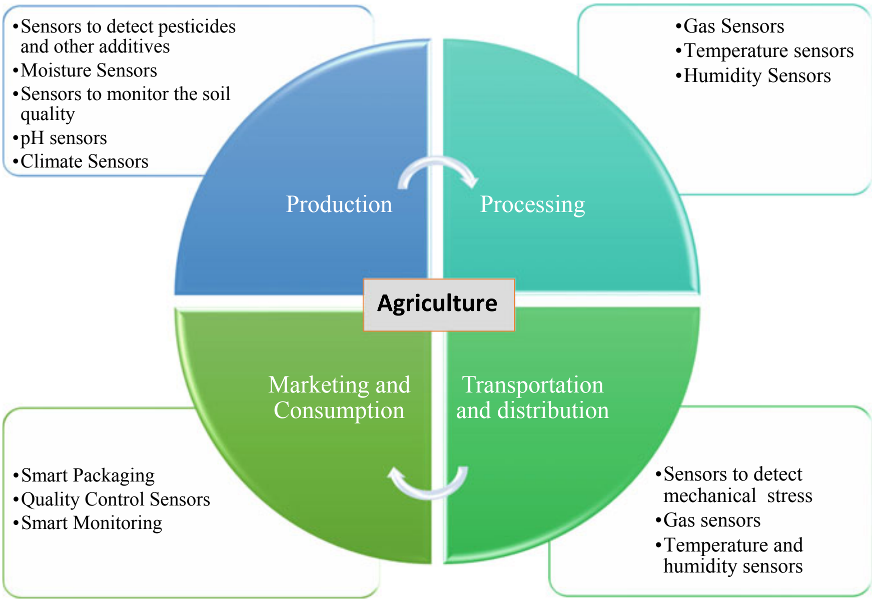
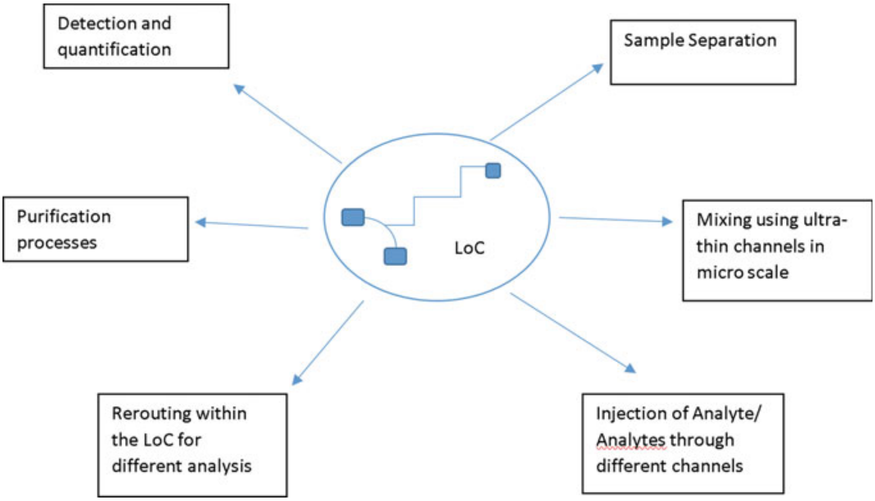


Fig. 26.5 Summary of application of sensors in agriculture



Scheme 26.1 Capabilities of a lab-on-chip device

for testing. The process itself is chemically cumbersome and time-consuming. Skilled labour and procuring expensive equipment augment to its cost, making it implausible, paving a way for microfluidic-based sensors which provide a versatile sensing platform requiring minimal amount of sample and providing rapid, accurate, inexpensive and easy to use results compared to the conventional techniques. By its miniaturization, the device allows for the use of lesser amounts of fluid for detection, and this greatly cuts reagent consumption costs, real-time monitoring is made possible and the resultant device itself is portable.

26.4.1 Advantages and Disadvantages of Microfluidic Devices

The ability of this technology to operate with very small volumes of sample makes it an ideal choice for the collection and analysis of samples. One can work with as little as a few microlitres of the analyte and make conclusive decisions. With the use of microfluidic (MF)-based devices, one can easily produce rapid, meaningful results. This enhances decision making when time is a constraint, as rapid, accurate results can be life-saving. Since the device itself is small, it is quite portable therefore, improving its mobility and applications in diverse situations and fields. These devices are easily disposable with little or no environmental consequences. Lower power consumption due to the reduced size of the device, higher surface-to-volume ratio and reduced Reynolds number are all some of the advantages of using microfluidic-based devices. Also, the ability to integrate with other devices impart more functionality within a single chip to carry out multiple functions and the relative ease of processing the derived results simultaneously, make microfluidic-based devices indispensable in every sphere of life.

Although MF-based devices offer a variety of advantages over conventional technologies, there are still a few challenges that need to be addressed. Manufacturing such devices on an industrial scale is still quite cumbersome and expensive. Integrating a lot of functionalities within a single device also raises concerns over cross-interference of the electrical components within the device. Since it operates with little volumes of sample, relative chance of error is quite high and therefore, one must carefully monitor each stage of the process of detection. Real-time monitoring is still a challenge and scientists are coming up with new and improved ways to compensate for these drawbacks, and one can summarize the advantages and disadvantages in a tabular column:

Advantages of microfluidic devices	Disadvantages of microfluidic devices
• Capable of working in small volumes • Reaction kinetics can be controlled with swifter responses and results • Low power consumption, portable due to miniaturization and better performance • Integration with different components to improve functionality of one device (LoC) • Relatively inexpensive since it consumes lower amounts of reagents	• Depending upon the complexity, the manufacturing cost of the final device model may be expensive • Requires cautious management of the device, although the processes within are automated • Real-time monitoring is still a challenge

26.5 Role of MF Sensors in Agriculture

The growing need to monitor various parameters within the field of agriculture has paved a way for the integration of novel nanomaterials to these sensing platforms. Nanomaterials are being widely researched in this regard owing to their unique properties due to high-surface-to-volume ratio compared to their bulk counterparts. This allows for fine-tuning of properties such as imparting chemical functionality and applicability in harsher environments where conventional sensors might fail, mechanical rigidity, etc. automatically enhancing the overall device capabilities (Soy et al. 2010). Use of these nanomaterials is further discussed in detail in the following sections.

There are plenty of processes involved in agriculture from crop production, to processing of the crop into edible components for consumption, transportation and distribution of these processed goods and ultimately marketing of the product and consumption by the consumers. Along each stage, careful monitoring is indispensable for the timely completion and delivery of processed product. To ensure high crop yield, farmers use top quality seeds which have been genetically improved to survive harsh environmental conditions. Although the seeds are robust, careful monitoring of the soil quality in which these seeds grow can provide information about the pH of the soil, whether it can sustain the growth of the seed, presence of contaminants, bacteria, pesticides, etc. This information can then be used to maximize crop production and thereby improving the yield. Sensors to detect the changes in climate, irrigation sensors to monitor water levels within the soil are all beneficial to boost overall production.

Once the crop has matured, it needs to be processed. Amid varied climatic and environmental conditions, farmers may have resorted to high amounts of pesticides, fungicides, fertilizers and external additives to improve crop yield. These toxins although augment production can be fatal if left untreated before reaching the consumers. Therefore, it is paramount to keep the concentrations of these toxic contaminants within the allowed residual limits. Hence, detection and quantification of these toxins at this stage is essential. These crops during processing can be susceptible to damage due to changes in temperature, cross-contamination during the various treatments in the processing step, variation in pH etc., consequently, installation of gas sensors to detect release of foul-smelling gases (H_2S sensors), temperature sensors to monitor and regulate temperature always are vital at this stage.

The processed goods need to then be delivered to consumers. This stage involves storage, transportation and distribution of the finished product. Parameters such as temperature, pH, humidity play a key role in determining whether the finished product is usable/consumable. Since this stage involves lot of mobility, the products need to be protected from external stress and shock. Sensors are employed to monitor the external forces acting on the product to ensure safe transport.

Sometimes, transport vehicles need to traverse through large distances with varying climatic conditions, and this raises concerns about the temperature conditions in which the product needs to sustain without being damaged or spoiled. Temperature sensors, humidity and gas sensors with easy-to-read output is necessary. Tracking of the goods with the help of RFIDs is also being widely used (Mainetti et al. 2013).

All these processes occur over prolonged periods of time, over which the resultant product is subjected to a wide variety of chemicals before finally being delivered into the market for consumption. Sensors are used to make existing materials smart by providing information about the product inside the packaged material. With a colorimetric indicator, it is possible to determine whether the product in concern is edible. Specific sensors to monitor the quality of the product are in great demand. Packaging of the product with materials that can give information about the freshness and quality of the packaged product are being widely sought (Fig. 26.5).

Along with this, the field of agriculture has been menaced by food-borne pathogenic agents, pesticides (such as organophosphates (OPs) and carbamates), heavy metals, veterinary drugs and various other illegal additives that some farmers utilize to improve crop yield. These harmful substances make their way into our food posing health risks owing to their toxic nature. Thus, and so, the detection of such toxic substances has become priority. To ensure the continuous production of good quality crops, a sensing platform needs to be implemented capable of accurately detecting with utmost sensitivity and selectivity, these toxic components (Fig. 26.6).

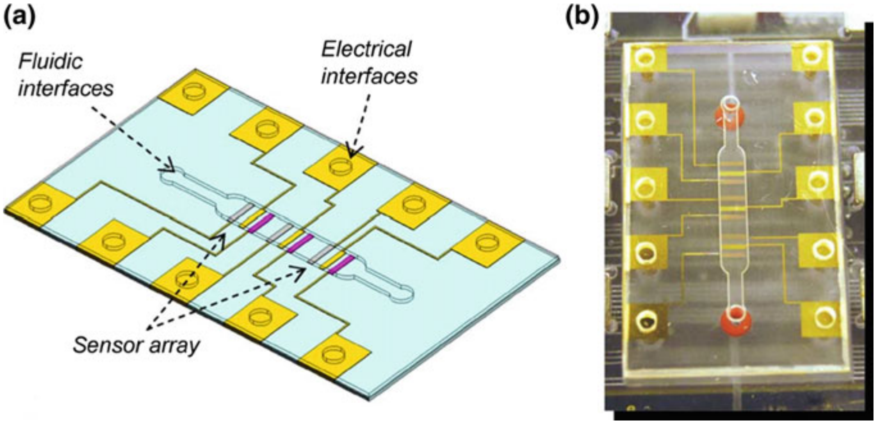


Fig. 26.6 **a** Schematic view of lab-on-a-chip array and **b** top view of the fabricated chip (Zou et al. 2009)

26.5.1 Detection of Pesticides Using Microfluidic Devices

Pesticides and insecticides are widely used materials in agriculture which are used to protect food crops from pests and insects. But the overuse of pesticides above its maximum residual limits causes inhibition of acetylcholinesterase enzyme which results in various neurological disorders, respiratory diseases and even death (Colovic et al. 2013). Microfluidic devices provide a versatile platform to detect these toxins in food chain rapidly with good sensitivity and selectivity. MF device consisting of microchamber detection inlet and a microchannel outlet using PDMS to sense pesticide residues in real vegetable samples was reported. The device was nothing but an interdigitated array of gold micro-electrodes capable of detecting chlorpyrifos with low limit of detection (LoD) in leek, lettuce and cabbage (Guo et al. 2015). In another study, a Botulinum neurotoxins (BoNTs) which are extremely toxic has been detected, using the device made of 96-well microfluidic immunoassay plate with a tapered spiral microchannel for each well capable of detecting sample volumes as less as 5 μL. The microchannel provided an enlarged surface are for quicker reaction kinetics (Babrak et al. 2016). Some of the work on use of biosensor for pesticides based on acetylcholinesterase is summarized in Table 26.2.

Table 26.2 A comparison of various electrochemical sensors for chlorpyrifos detection

Electrode[a]	Linear range	Response time	Reference
Au/ssDNA-SWCNT/PANI/AChE	1.0×10^{-11}–1.0×10^{-6} M	15 min	Viswanathan et al. (2009)
GC-MWCNT-CoPc	0.33–6.61 μmol/L	–	Moraes et al. (2009)
AChE-TCNQ-PVA-SbQ	–	–	Nunes et al. (2004)
AChE/PAMAM-Au/CNTs	4.8×10^{-9}–0.9×10^{-7} M	–	Qu et al. (2010)
AChE/Au/Chi	0.004–24 μg/mL	10 min	Li et al. (2011)
[BMIM][BF4]/MWCNT-CP	10^{-8}–10^{-6} M	15 min	Zamfir et al. (2011)
AChE-CdS-G-CHIT-GCE	2 ng/mL–2 g/mL	2 min	Wang et al. (2011)
AChE/PB-CHIT/GCE	0.01–0.4 μM	300 s	Song et al. (2011)
AChE/MWCNTs-SnO_2-CHIT/SPE	0.05 μg/L	–	Chen et al. (2015)

[a] *Au* gold, *ssDNA* single-stranded DNA, *SWCNT* single-walled carbon nanotubes, *PANI* polyaniline, *AChE* acetylcholineesterase, *GC/GCE* glassy carbon electrode, *MWCNT* multi-walled carbon nanotube, *CHIT* chitosan, *CdS* cadmium sulphide, SnO_2 tin oxide, *SPE* screen-printed electrode, *PB-CHIT* prussian blue modified chitosan, *BMIM* BF_4 1-butyl-3-methylimidazolium tetrafluoroborate, *CoPc* cobalt phthalocyanine, *TCNQ* 7,7,8,8-tetracyanoquinodimethane, *PVA* poly(vinyl alcohol), *SbQ* styrylpyridinium groups and *PAMAM* polyamidoamine

26.5.2 Detection of Pathogens and Mycotoxins Using Microfluidic Devices

Pathogens such as *Escherichia coli, Salmonella, Listeria, Campylobacter jejuni, Shigella* are predominant in food and have been responsible for severe health hazards around the world (Priyanka et al. 2016). Diseases such as acute emesis and acute abdominalgia are caused due to the contamination of food by the presence of these pathogens (Lv et al. 2018). To curb these toxic effects in food, detection of these pathogens is imperative. Conventionally, this can be accomplished by culturing the bacteria onto agar plates which is laborious and time-consuming. With the advent of microfluidic-based sensing, a rapid, relatively inexpensive and accurate detection of these toxins can be achieved (Fig. 26.7). A variety of nanomaterials have been employed to facilitate this detection (Lv et al. 2018; Mustafa et al. 2017; Zhang et al. 2018).

Wang and co-workers used gold nanorods to detect genetically altered *E. coli* strain expressing green fluorescent protein with the help of a simple Polymethylmethacrylate (PMMA)-based microfluidic device (Fig. 26.7). The applicability of this device was tested in PBS, milk and spinach samples, and the respective LOD was found to be 50, 50 and 500 CFUs/mL, respectively (Wang et al. 2012). Tan and co-workers developed a PDMS-based flow-through type immunosensor of antibody immobilized nanoporous alumina membrane. The LOD as tested in a PBS solution against food pathogens *S. aureus* and *E. coli* was reported to be 10^2 CFU/mL (Tan et al. 2011). An eight-channel microfluidic device for the detection of Staphylococcal Enterotoxin B (SEB) fabricated by Yang and colleagues received much attention as it utilized lamination technology for a six-layer black acrylic based MF device (Yang et al. 2010). A mixture of the anti-SEB antibody and carbon nanotubes (CNTs) immobilized onto a polycarbonate strip was reported to study and quantify simultaneously eight samples at a time. A microsyringe was used to install the flow of sample fluids within the device achieving a limit of detection of 0.1 ng/mL in soy milk (Yang et al. 2010). Quantum dots (QDs) are also being extensively researched in the biomedical field as they exhibit extraordinary optical properties. QD-aptamer-based conjugate for the detection of *Campylobacter jejuni* was described in one study. It was possible to detect dead as well as live bacteria within buffer and various other food systems (Bruno et al. 2009).

Mycotoxins are secondary metabolites released by fungi and are known to cause several health complications. Aflatoxin B1, zearalenone (ZEA), citrinin (CIT), ochratoxin-A (OTA), etc. are poisonous metabolites from fungi that pollute food and are a cause for concern (Alassane-Kpembi et al. 2017). Hu et al. demonstrated serpentine-shaped microfluidic channels to detect low concentrations of aflatoxin B1 in corn extract samples with the help of smectite–polyacrylamide nanocomposite on glass slides. In order to facilitate quick adsorption of aflatoxin, these serpentine-shaped channels helped reduce the diffusion path (Hu et al. 2013). Hervás et al. devised two schemes for the detection of mycotoxin zearalenone

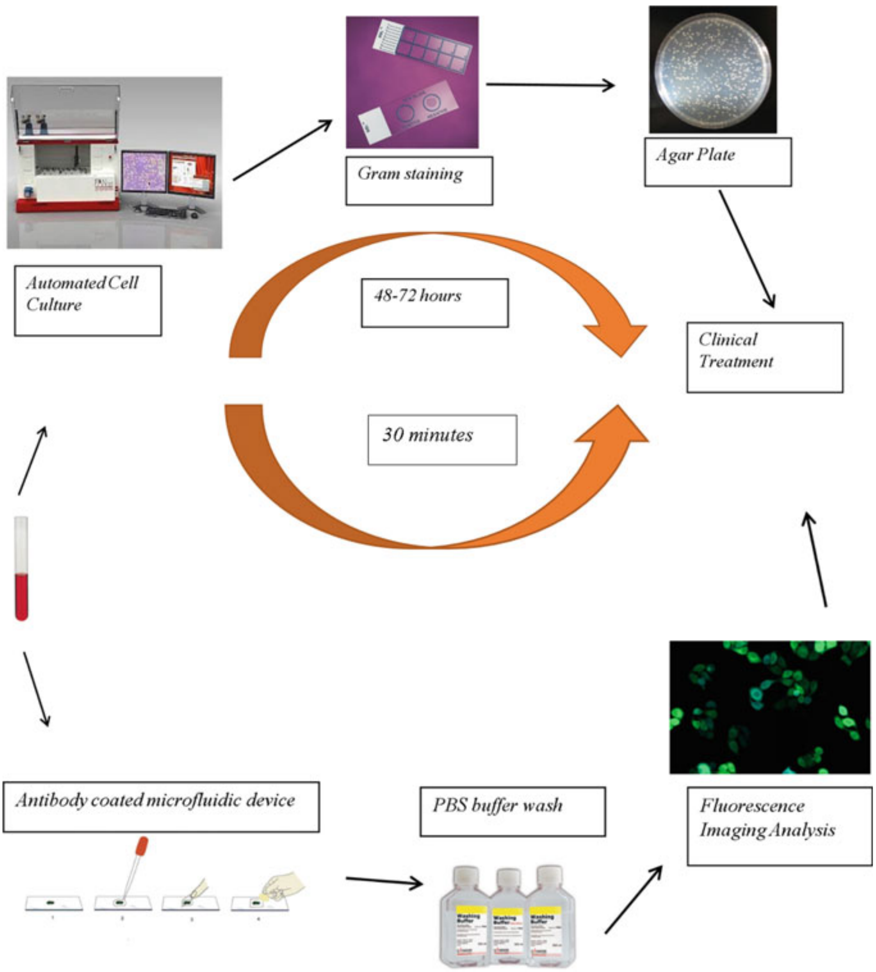


Fig. 26.7 **a** Conventional culture method for pathogen detection versus **b** PoC approach for rapid and accurate results (Wang et al. 2012)

(ZEA) in foods. A microchip made of glass along with four-way injection cross, a longitudinal channel with relative length and short side arms was used to detect less than 1 ppb of ZEA within a timespan of approximately 200 s (Hervás et al. 2011). The other approach involved fabrication of a double-T-mixing junction aimed at performing immune and enzymatic interaction. A limit of detection of 0.4 µg/L was reported for ZEA present in maize sample taking approximately 15 min for the entire reaction (Rodrigues et al. 2015). Another study demonstrated a microfluidic channel consisting of metallic nanostructures embedded within PDMS microchannel for the detection of ochratoxin-A (OTA) (Galarreta et al. 2013).

26.5.3 Detection of Heavy Metals

Pollutants within food are not just limited to pathogens but also presence of heavy metallic components beyond threshold levels of concentrations can have adverse effects on human health. Ingestion of metal ions such as Hg^{2+}, Cd^{2+}, Pb $^{2+}$, etc. are primary causes for many neural disorders, deficits in cognitive ability and in lethal cases death (Chen et al. 2016). Detection and quantification of these heavy metal ions thus becomes a crucial factor in controlling toxicity from food.

Colorimetric sensors using gold nanoparticles (AuNPs) for the detection of Hg^{2+} were developed. Thymine is known to have a specific affinity for Hg^{2+}, and this was exploited by Chen and his co-workers to create a paper-based microfluidic platform for the detection of Hg^{2+} through the coordination of T-Hg^{2+}-T. The colour change was a direct consequence of AuNP aggregation (Chen et al. 2014). Surface-enhanced Raman scattering (SERS) sensor was reported by Yin et al. for the detection of Cd^{2+} owing to the selective self-aggregation of AuNPs due to the interparticle plasmonic coupling in presence of Cd^{2+} (Yin et al. 2011). A catalytic hairpin assembly capable of synergistically amplifying the specific detection of Pb^{2+} was demonstrated in another study. This electrochemical biosensor detected Pb^{2+} by DNAzymes specific to Pb^{2+}, thereby inducing a replacement reaction on the strand leading to the formation of a dendritic structure of DNA on the surface of the electrode (Zhao et al. 2008). Pt@Pd nanocages and electro-active toluidine blue was captured on the electrode surface due to hybridization of DNA, forming a dendritic structure in order to facilitate manganese(III)meso-tetrakis(4-*N*-methyl-pyriniumyl)-porphyrin (MnTMPyP) immobilization. Synergistic catalysis of Pt@Pd nanocages and MnTMPyP to H_2O_2 reduction induced a signal enhancement in the detection of Pb^{2+} (Zhao et al. 2017).

26.5.4 Detection of Veterinary Drugs

Veterinary drugs control infections caused by bacteria and prevent outbreak of diseases in livestock. Due to the accumulation of these drug metabolites in products of the livestock such as meat, eggs and milk, a plethora of cases citing the ill effects on consumers has been reported (Baynes et al. 2016; Reig and Toldrá 2008). A quantity termed maximum residue limit (MRLs) has been established for drugs such as antibiotics, anti-helmintics, hormonal drugs, sulpha drugs, which defines the maximum allowed concentration of these drugs in food. Food quality control calls for the detection and quantification of these veterinary drugs. A one-step strip test method for the detection of streptomycin using AuNPs coated with the corresponding monoclonal anti-streptomycin antibodies was utilized to screen for residues from veterinary drugs in raw milk (Verheijen et al. 2000). In another study, an indirect competitive fluorescence-linked immunosorbent assay (cFLISA) was used in the detection of sulphamethzine (SM_2) in the muscle tissue of chickens.

QDs were deployed as fluorescence labels coupled with a secondary antibody (Ding et al. 2006). A similar method demonstrated by was applied to detect enrofloxacin (Chen and Wu 2012). An electrochemical biosensor consisting of molybdenum disulphide nanosheets coated onto a well-functionalized MWCNT to determine chloramphenicol (CAP) was also been developed. The electrode which was modified with the nanocomposite showed preferential electro-catalytic activity to CAP and provided accurate results over a wide linear concentration ranging from 0.08 to 1392 μM (Govindasamy et al. 2017).

26.5.5 Detection of Illegal Additives

There has been an overwhelming rise in the abuse of illegal additives in the food industry due to the increasing demands of the growing population as well as continuous competition. This poses a threat to health and raises questions about the quality and safety of food. Typically, melamine, clenbuterol and Sudan I are commonly used. Overuse of such additives can cause irreversible damage to human health.

Melamine is illegally used in flame-retardants, in textile industries, in the production of pesticides, as an adulterant in milk and pet food due to its economic viability and it being a natural source for high nitrogen content. Renal failures and sometimes death in infants are induced when ingested with melamine beyond the safety limit (Guan et al. 2009). A real-time detection of melamine in milk products using AuNPs modified with 1-(2-mercaptoethyl)-1,3,5-triazinane-2,4,6-trione (MTT) has been demonstrated. When melamine was present in the detection system, the AuNPs aggregated causing a colour change from wine red to purple. This was because of the hydrogen bonding between melamine and MTT causing AuNPs to aggregate (Ai et al. 2009) (Fig. 26.8).

A similar method was adopted by Ma et al. to detect melamine using dopamine-stabilized AgNps (Ma et al. 2011). Here, the reduction of Ag^+ ions to AgNps was facilitated by dopamine. The melamine which coexists in the reaction solution leads to a colorimetric response induced from the aggregation of silver nanoparticles because of melamine–dopamine binding. In this manner, the overall intensity of the colour change can be a direct correlation to the melamine concentration which was in the range of 10 ppb to 1.26 ppm. Clenbuterol is a banned drug which is used as a nutrient agent in most livestock. A surface plasmon resonance (SPR)-based biosensor used AuNPs labelled antibody for the detection of Clenbuterol. This immunosensor was found to have a limit of detection of 0.05 pg/mL (Kabiraz et al. 2017) (Fig. 26.8).

Sudan 1 is a bright red carcinogen widely used as a food additive due to its low cost. The detection of Sudan 1 in two previous studies utilized the adsorption properties of MWCNTs and their large surface area. The electrode itself was modified with CNT for the successful detection of Sudan 1 (Gan et al. 2008; Mo et al. 2010). The recent study utilized Pt NPs conjugated with graphene

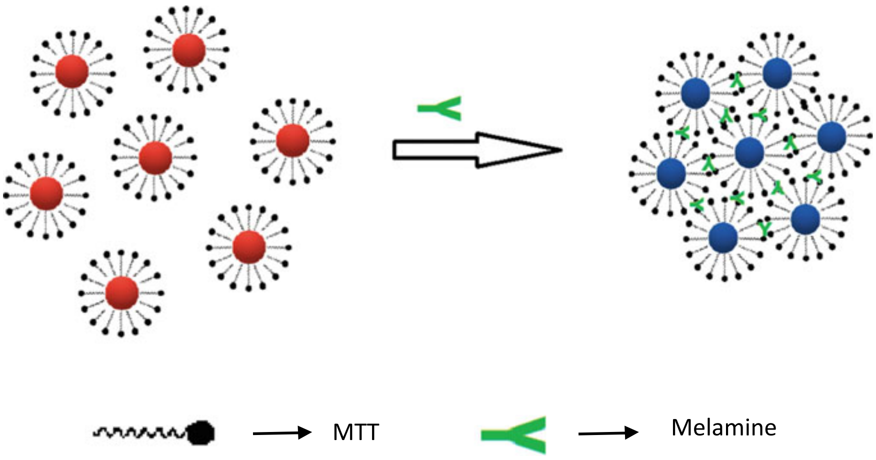


Fig. 26.8 Colorimetric detection of melamine using the MTT-stabilized gold (Ai et al. 2009)

β-cyclodextrin modified electrode study for detection of Sudan 1 (Palanisamy et al. 2017).

Bisphenol-A (BPA) a phenolic compound is a toxic pollutant in water, soil and food due to its disruptive endocrine activity (Canesi and Fabbri 2015). Plastic packaging involves use of this BPA as an additive and therefore requires quantification. Recent study by our group had demonstrated an MnO_2-based electrochemical sensor for the detection of BPA using a microfluidic device. BPA concentration was determined in ethanol employing nano-MnO_2 as a receptor. The LOD was estimated to be 0.66 μM (Khanna et al. 2018) (Fig. 26.9).

26.6 Current Status and Prospects

Paper-based microfluidics have opened further possibilities in this field owing to its feasibility. These low-cost, portable and disposable electrodes for real-time monitoring are a perfect replacement for conventional electrodes. A fluorescence-based microfluidic device for the detection of *Lactobacillus acidophilus*, *Staphylococcus aureus* and *Salmonella enterica* has been developed in previous study involving a PDMS/paper/glass hybrid system for device fabrication. The set-up employed a graphene oxide and aptamer-based biosensor reporting an overall limit of detection of 11.0 CFU/mL (Zuo et al. 2013). An electrochemical paper-based analytical device (EPAD) developed for the detection of *S. aureus* incorporated use of graphene nanodots (GNDs) and zeolite using a specific DNA probe. This resulting ssDNA/GNDs-Zeo modified genosensor with a LOD of 0.1 nM offered a low-cost, highly specific alternative to conventional sensors with analysis time of about 10 s for results (Mathur et al. 2018) (Fig. 26.10).

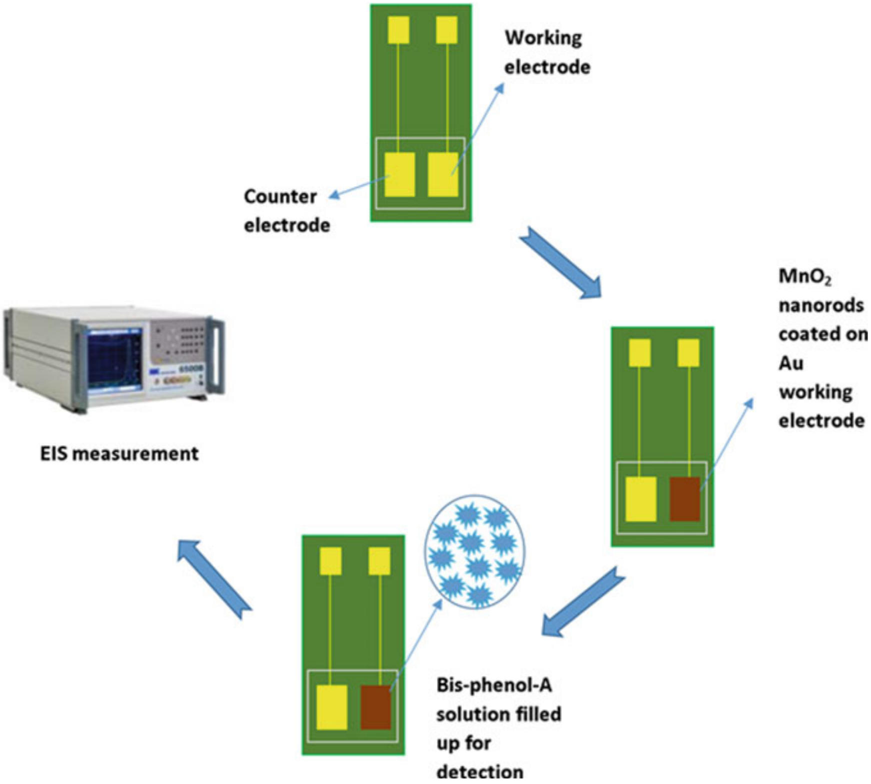


Fig. 26.9 Schematic representing the different steps involved in the preparation of PCB electrode deployed for Bisphenol-A detection using EIS measurements (Khanna et al. 2018)

Current research is on to integrate and enable portable, fast devices capable of carrying out multiple tasks and report results accurately. Over the past few decades, there has been a tremendous leap in the electronics sector leading to a dramatic development in smart phone technologies. A combination of this multi-functionality to monitor and control various parameters such as soil quality, irrigation check for example the amount of water intake by crops, detection of toxins and additives etc. with a simple interface that can transmit information to your handheld device will immensely impact crop yield.

The relatively inexpensive paper-based microfluidic technology could mightily revolutionize the existing agricultural practices and therefore enhance quality of life for humans. There are still plenty of challenges to think about before deploying paper-based microfluidic devices for different applications. Although inexpensive, the paper itself is quite tangible and current fabrication practices for paper-based devices do not offer high resolution. This may even damage the properties of the paper during the process of fabrication. Multiple detection strategies have been studied such as colorimetric, fluorescence, chemiluminescence and electrochemical detection, each of which comes with a set of advantages and disadvantages.

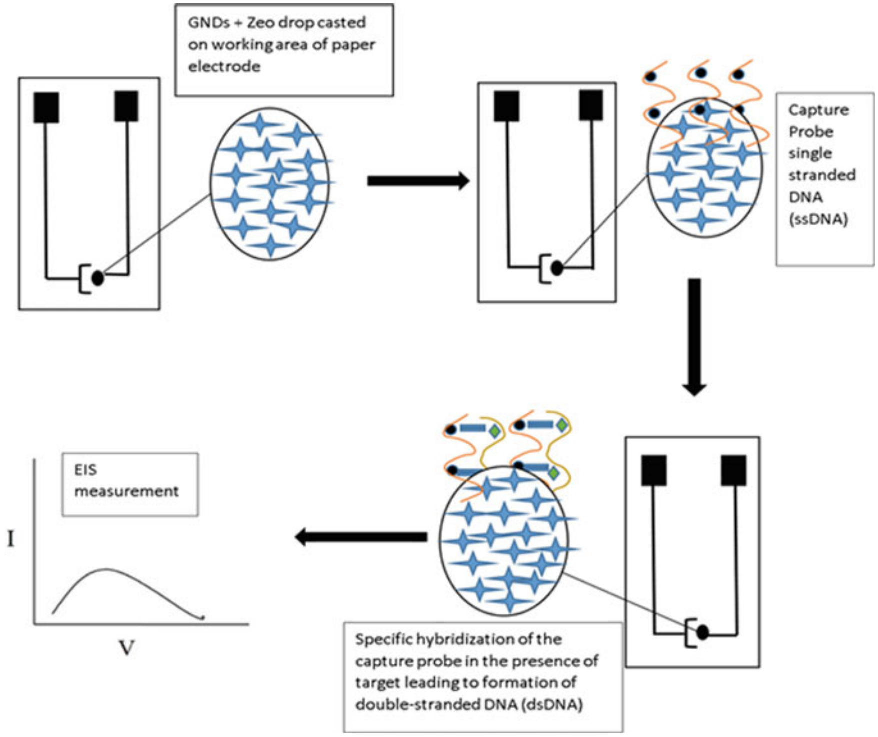


Fig. 26.10 Fabrication of the GNDs-Zeo modified PAD, ssDNA/GNDs-Zeo/PAD and dsDNA/GNDs-Zeo/PAD (Mathur et al. 2018)

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Chapter 27
Nanotechnology Applications in Food: A Scientometric Overview

Ozcan Konur

Abstract Both the food science and technology and nanoscience and nanotechnology have been a basic component of the scientific literature with over one million indexed papers each since 1980s. In the meantime, scientometrics has emerged as a new interdisciplinary scientific discipline since 1960s. This scientometric tool has been applied both to nanoscience and nanotechnology and to food science and technology. However, there has been no application of the scientometric tool to the nanotechnology applications in foods in general, although there have been two studies focusing on food nanopreservation and nanoemulsions used in the food industry. This study aims to apply the scientometric tool to the nanotechnology applications in foods in general to provide information for the stakeholders in the light of the new institutional theory, focusing on 53 citation classics forming the top 1% of the indexed papers published in this novel research field as a first-ever study for the food science and technology. The results show that the reviews were significantly over-represented in these classical papers. The most-prolific subjects were 'nanotechnology applications in food emulsions' and 'nanotechnology applications in food packaging' with 13 papers each. These 2 top subjects were followed by 'nanotechnology applications in encapsulation of foods', 'nanotechnology applications in food safety', and 'other nanotechnology applications in foods' with 7 papers each. Additionally, there were 6 papers in nanotechnology applications in foods in general. It is notable that these citation classics focused on the structure–processing–property relationships as in other scientific disciplines such as nanoscience and nanotechnology, food science and technology, and materials science and engineering. The most-prolific author was 'David Julian McClements' of University Massachusetts at Amherst of the USA with 6 papers, and there was a significant gender deficit among the authors. The USA was the most-prolific county publishing 19 papers, 36% of the sample whilst the University of Massachusetts at Amherst was the most-prolific institution with 7 papers. Only 20 citation classics (38%) declared any source of funding and 64 funding bodies

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were acknowledged as a source of funding in the remaining 33 papers. These classical papers were published between 2005 and 2013, and the most-prolific publication years were 2008 and 2009 with 10 papers each. The most-prolific 3 journals related to food science and technology, Food Chemistry, Food Hydrocolloids, and Trends in Food Science Technology, had 4 papers each. As expected, 'Food Science and Technology' was the most-prolific subject category indexing 31 papers, 58.5% of the sample. The citation impact of these citation classics was significant as there were 14,624 citations received for these papers in total. The average number of citations per paper was 276.23, and *h*-index was 53. Thus, these citation classics contributed to the scientific literature at large. The results show that the scientometric tool has a great capacity to provide timely and detailed information about 53 citation classics forming the top 1% of the original sample of 5340 papers in line with the teaching of the new institutional theory for the key stakeholders.

Keywords Food science and technology · Nanoscience and nanotechnology · Food emulsions · Food encapsulations · Food packaging · Food health and safety · Scientometrics · Citation classics · Gender deficit · Citation analysis · New institutional theory

27.1 Introduction

The food science and technology has been a basic component of the scientific literature with over one million indexed papers since 1980s (Brand-Williams et al. 1995; Burt 2004; Manach et al. 2004; Mead et al. 1999). Similarly, the nanoscience and nanotechnology has been a basic component of the scientific literature with over one million indexed papers since 1980s (Baughman et al. 2002; Chen and Mao 2007; Daniel and Astruc 2004; Lee et al. 2008; Novoselov et al. 2005). In the meantime, scientometrics has emerged as a new interdisciplinary scientific discipline since 1960s (Garfield 1964, 1972, 1979, 2006). This scientometric tool has been applied both to nanoscience and nanotechnology (Hullmann and Meyer 2003; Konur 2016a, b, c, d, e, f, g, 2017a, b, c, d; Kostoff et al. 2006; Schummer 2004; Youtie et al. 2008) and to food science and technology (Alfaraz and Calvino 2004; Borsi and Schubert 2011; van Raan and van Leeuwen 2002; Zhou et al. 2013). Similarly, the 'new institutional theory' has emerged as an interdisciplinary analytical tool since 1960s (North 1991, 1994; Denzau and North 1994). This tool has been applied to social sciences (Konur 2000, 2002a, b, c, 2004, 2006a, b, 2007a, b, 2012a, 2013a).

However, there has been no application of the scientometric tool to the nanotechnology applications in foods in general, although there have been 2 studies focusing on food nanopreservation and nanoemulsions used in the food industry (Konur 2016a, b). This study aims to apply scientometric tool to the nanotechnology applications in foods in general focusing on 53 citation classics forming the top 1% of the indexed papers published in this novel research field as a first-ever study for the food science and technology.

27.2 Methods and Materials

A multi-step search strategy was employed in this study using the Science Citation Index Expanded (SCIE), Social Sciences Citation Index (SSCI), and Arts and Humanities Citation Index (A and HCI) in June 2018. As in the other topical scientometric studies (Konur 2011a, b, 2012b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, 2013b, c, d, e, f, g, h, i, 2014a, b, 2015a, b, c, d, e, f, g, h, i, j, k, l, m, 2016h, i, 2017e, 2018a, b), the most-crucial step is the development of an optimised topical keyword set. For this purpose, the developed keyword set is given below.

> (TI = (*Food* or *nutraceut* or “beta carotene*” or “essential oil*” or nutrition* or milk or dairy or edible or meat or poultry or “soft drink*” or beef or beverage* or fruits or eggs) or OG = (food* or nutr or dairy) or SO = (“acta alimenteria” or “advances in nutr*” or “agricultral and food*” or “agro food*” or “annual review of food*” or “annual review of nutr*” or appetite or “australian journal of grape*” or “british food*” or “british journal of nutr*” or cereal* or “ciencia e tecnica vitinicola” or “clinical nutr*” or “comprehensive reviews in food*” or “critical reviews in food*” or “current opinion in food*” or cyta* or “czech journal of food*” or dairy* or “ecology of food*” or “emirates journal of food*” or “european food*” or “european journal of nutr*” or foodborne* or “global food*” or “international dairy*” or “innovative food*” or “international food*” or “international journal of dairy*” or “international journal of food*” or “irish journal of agriculture and food*” or “italian journal of food*” or “journal of agricultural and food*” or “journal of aquatic food*” or “journal of cereal*” or “journal of consumer protection and food” or “journal of dairy*” or “journal of essential oil*” or “journal of food*” or “journal of functional foods” or “journal of human nutr*” or “journal of medicinal food*” or “journal of nutr*” or “journal of the science of food*” or “korean journal for food*” or “lwt food*” or “meat science” or milchwissenschaft* or “molecular nutrition food*” or nahrung or nutrit* or “oeno one” or “plant food*” or “polish journal of food*” or poultry* or “progress in nutr*” or “quality assurance and safety of crops foods” or “renewable agriculture and food*” or “trends in food*” or food* or “world review of nutr*”)) and (TI = (nano* or bionano* or “quantum dots” or graphene or fullerene*) or OG = (nano*))
>
> 5915

This keyword set includes the sub-keyword sets for titles, organizations and source titles for the food topical area, whereas it includes sub-keyword sets only for titles and organizations for the nanotechnology topical area.

Additionally, a secondary keyword set is developed to exclude unrelated references as given below.

> TI = (“food chain*” or “food web*” or “human milk” or *flagell* or castor or biocl or *plankton or “food effect*” or serum or nano2 or sludge or daphnia or dyes or fuel* or thought or stem or *diesel or pentagon or cytotoxic* or nanotoxicity)
>
> 856152

A quality control exercise was carried out to ensure that the found references were related to the nanofood with a 'hit rate' of near 100%. The quality control is a crucial element in all scientific disciplines (Anderson et al. 2010; Patel and Jain 2012; Teppo et al. 1994). The original research sample was refined for the document types of article, review, note, and letter and the language of English.

Next, the top 53 most-cited papers, forming the top 1% of the sample, were selected for the analysis. The data was collected on the authors, documents, organizations, countries, publication years, funding bodies, source titles, subject categories for this refined research sample. Additionally, the data on the citation impact of the refined research sample was collected.

27.3 Documents

The search using the optimised keyword set given in the above section gave 5683 papers. When this sample was refined for the document type (article, review, editorial, letter, and note) and language (English), the number of papers in the sample fell to 5340 papers. This sample of 5340 papers is designated as 'original sample' in this study. There were 53 papers in the top 1% based on the number of citations received. These papers are designated as 'citation classics'.

There were 32 and 21 'articles' and 'reviews' in this sample, forming 58.5 and 41.5% of the sample, respectively. It is notable at the first sight that the percentage of reviews is unusually very high. Four of these papers were also classed as 'proceedings papers' as they were presented in the conferences. It is notable that there was no 'retracted paper' in these citation classics (Fang et al. 2012; He 2013; Steen et al. 2013). In contrast, articles and reviews formed 92.2 and 6.3% of the original paper sample, respectively. Thus, it appears that reviews were significantly over-represented in the citation classics. Similarly, editorial materials and letters were not represented in the citation classics as they formed 1.3 and 0.1% of the original paper sample, respectively.

27.4 Topical Areas of Citation Classics

These citation classics were grouped under 6 topical areas to gain the understanding of the development of the research in the applications of nanotechnology in foods. The most-prolific subjects were 'nanotechnology applications in food emulsions' and 'nanotechnology applications in food packaging' with 13 papers each. These 2 top subjects were followed by 'nanotechnology applications in encapsulation of foods', 'nanotechnology applications in food safety', and 'other nanotechnology applications in foods' with 7 papers each. Additionally, there were 6 papers in nanotechnology applications in foods in general.

It is notable that these citation classics focus on the structure–processing–property relationships as in other scientific disciplines such as nanoscience and nanotechnology, food science and technology, and materials science and engineering (Konur and Matthews 1989; Mishra et al. 2009; Ostuni et al. 2001; Scherf and List 2002).

The papers in ‘nanotechnology applications in foods in general’, outlined in Table 27.1, relate to the general discussion of the nanotechnology applications in foods covering major areas of research such as food packaging, food safety, emulsions, encapsulations, and other applications. The most-prolific paper was a paper by Chaudhry et al. (2008) with total 463 citations and 59 citations per year. Weiss et al. (2006) provided an overview of applications of nanotechnology in food industry with 31 citations per year whilst Acosta (2009) provided an overview of nanoparticle delivery systems for nutrients and nutraceuticals with 41 citations per year. Sozer and Kokini (2009) provided an overview of nanotechnology applications in foods with 35 citations per year whilst Sanguansri and Augustin (2006) and Cushen et al. (2012) provided an overview of nanotechnology applications in foods with 26 and 35 citations per year, respectively.

It is notable that all these papers, published in journals related to food science and technology between 2006 and 2012, were reviews and the average number of citations was 311. These papers were instrumental in increasing public awareness about the nanotechnology applications in foods. Four of the lead authors were male. The average number of pages per paper and number of references per paper were 13 and 77, respectively. The most-prolific country was the USA with 2 papers.

The papers in ‘nanotechnology applications in food emulsions’, outlined in Table 27.2, relate to the development and discussion of the nanotechnology applications in food emulsions. The most-prolific paper was a paper by McClements and Rao (2011) on the overview of food-grade nanoemulsions with 356 citations and 59 citations per year. McClements (2011) provided an overview of edible nanoemulsions with 52 citations per year whilst Qian and McClements (2011) and Wooster et al. (2008) determined nanoemulsion formation with 47 and 38 citations per year, respectively. Huang et al. (2010) provided an overview of nanodelivery of nutraceuticals with 38 citations per year whilst Kentish et al. (2008) prepared food nanoemulsions by ultrasonics with 26 citations per year and Yuan et al. (2008) and Tan and Nakajima (2005) studied the development of β-carotene nanoemulsions with 22 and 16 citations per year, respectively.

Dickinson (2012) provided an overview of β-carotene nanoemulsions with 38 citations per year whilst Wang et al. (2008) and Tzoumaki et al. (2011) studied the development of curcumin nanoemulsions and nanoemulsions in general with 20 and 29 citations per year, respectively. Ahmed et al. (2012) studied the development of nanoemulsions for curcumin whilst Weiss et al. (2008) provided an overview of applications of solid lipid particles in foods with 34 and 19 citations per year, respectively.

It is notable that all these papers, published mostly in journals related to food science and technology between 2005 and 2012, were mostly articles and the average number of citations was 231. These papers were instrumental in increasing

Table 27.1 Citation classics in nanotechnology applications in foods in general

	Author	Year	Doc.	Insts.	Country	NA	AG	Lead author	LA RA	NP	NR	Journal	Subject	Topic	Cits1	Cits2
3	Chaudhry et al.	2008	R	Univ. York +2	England, Scotland	8	M	Chaudhry, Qasim	Univ. Chester	18	58	Food Addit. Contam. Part A-Chem.	Chem. Appl., Food Sci. Tech. +1	Overview of nanotechnology applications in food in general	463	51
11	Weiss et al.	2006	R	Univ. Massachusetts, Rutgers State Univ.	US	3	M	McClements, David Julian	Univ. Massachusetts	10	58	J. Food Sci.	Food Sci. Technol.	Overview of applications of nanotechnology in food industry	337	31
14	Acosta	2009	R	Univ. Toronto	Canada	1	M	Acosta, Edgar	Univ. Toronto	13	92	Curr. Opin. Colloid Interface Sci.	Chem. Phys.	Overview of nanoparticle delivery systems for nutrients and nutraceuticals	326	41
21	Sozer and Kokini	2009	R	Ill. Agr. Expt. Stn.	US	2	F	Kokini, Jozef L	Purdue Univ.	8	76	Trends Biotechnol.	Biot. Appl. Microb.	Overview of nanotechnology applications in foods	282	35
22	Sanguansri and Augustin	2006	R	CSIRO	Australia	2	M	Augustin, Mary Ann F	CSIRO	10	72	Trends Food Sci. Technol.	Food Sci. Technol.	Overview of nanotechnology application in foods	281	26
47	Cushen et al.	2012	R	Univ. Coll. Dublin, Natl Univ. Ireland Univ. Coll. Cork	Ireland	5	F	Cummins, Enda M	Univ. Coll. Dublin	17	108	Trends Food Sci. Technol.	Food Sci. Technol.	Overview of nanotechnology applications in foods	175	35

Doc document type, *A* article, *R* review, *NA* number of authors, *AG* author gender, *F* female, *M* male, *LA RA* lead authors' current institution, *NP* number of pages, *NR* number of references, *Subject* subject category of journals designated by the databases, *Cits1* the total number of citations received, *Cits2* the average number of citations per year

Table 27.2 Citation classics in nanotechnology applications in food emulsions

	Author	Year	Doc.	Insts.	Country	NA	AG	Lead author	LA RA	NP	NR	Journal	Subject	Topic	Cits1	Cits2
10	McClements and Rao	2011	R	Univ. Massachusetts	US	2	M	McClements, David Julian	Univ. Massachusetts	46	206	Crit. Rev. Food Sci. Nutr.	Food Sci. Technol., Nutr. Diet.	Overview of food-grade nanoemulsions	356	59
16	McClements	2011	R	Univ. Massachusetts	US	1	M	McClements, David Julian	Univ. Massachusetts	20	127	Soft Matter	Chem. Phys., Polym. Sci. +2	Overview of edible nanoemulsions	310	52
19	Qian and McClements	2011	A	Univ. Massachusetts	US	2	M	McClements, David Julian	Univ. Massachusetts	9	47	Food Hydrocolloids	Food Sci. Technol., Chem. Appl.	Determination of nanoemulsion formation	283	47
24	Wooster et al.	2008	A	CSIRO	Australia	3	M	Golding, Matt	Massey Univ.	8	39	Langmuir	Chem. Mult.; Chem. Phys. +1	Determination of nanoemulsion formation	271	30
26	Huang et al.	2010	R	Rutgers State Univ.	US	3	M	Huang, Qinrong	Rutgers State Univ.	8	72	J. Food Sci.	Food Sci. Technol.	Overview of nanodelivery of nutraceuticals	263	38
28	Kentish et al.	2008	A	Univ. Melbourne +1	Australia	6	F	Kentish, Sandra C F	Univ. Melbourne	6	18	Innov. Food Sci. Emerg. Technol.	Food Sci. Technol.	Nanoemulsion preparation by ultrasonics	236	26
39	Yuan et al.	2008	A	China Agr. Univ., Charles Sturt Univ.	China, Australia	4	M	Gao, Yanxiang	China Agr. Univ.	8	18	Food Res. Int.	Food Sci. Technol.	Development of β-carotene nanoemulsions	197	22
41	Tan and Nakajima	2005	A	Natl. Food Res. Inst., Univ. Pertanian Malaysia	Malaysia, Japan	2	M	Nakajima, Mitsutoshi	Univ. Tsukuba	11	24	Food Chem.	Food Sci Technol., Chem. Appl. +1	Development of β-carotene nanoemulsions	191	16

(continued)

Table 27.2 (continued)

	Author	Year	Doc.	Insts.	Country	NA	AG	Lead author	LA RA	NP	NR	Journal	Subject	Topic	Cits1	Cits2
42	Dickinson	2012	R	Univ. Leeds	England	1	M	Dickinson, Eric	Univ. Leeds	9	64	Trends Food Sci. Technol.	Food Sci. Technol.	Overview of β-carotene nanoemulsions	189	38
46	Wang et al.	2008	A	Rutgers State Univ.	US	6	M	Ho, Chi-Tang	Rutgers Univ.	20	32	Food Chem.	Chem. Appl., Food sci. Tech.	Development of curcumin nanoemulsions	179	20
48	Tzoumaki et al.	2011	A	Aristotle Univ. Thessaloniki	Greece	4	F	Biliaderis, Costas G	Aristotle Univ. Thessaloniki	9	50	Food Hydrocolloids	Food Sci. Technol., Chem. Appl.	Development of nanoemulsions	174	29
53	Ahmed et al.	2012	A	Univ. Massachusetts	US	4	M	McClements, David Julian	Univ. Massachusetts	9	30	Food Chem.	Food sci. Technol., Chem. Appl. +1	Development of nanoemulsions for curcumin	171	34
51	Weiss et al.	2008	A	Univ. Massachusetts, Univ. Iceland	US, Iceland	6	M	McClements, David Julian	Univ. Massachusetts	9	97	Food Biophys.	Food Sci. Technol.	Overview of applications of solid lipid particles in foods	171	19

Doc document type, *A* article, *R* review, *NA* number of authors, *AG* author gender, *F* female, *M* male, *LA RA* lead authors' current institution, *NP* number of pages, *NR* number of references, *Subject* subject category of journals designated by the databases, *Cits1* the total number of citations received, *Cits2* the average number of citations per year

public awareness about the nanotechnology applications in food emulsions where the most-prolific lead author was McClements with 5 papers and all the lead authors were male. The average number of pages per paper and number of references per paper were 13 and 63, respectively. The most-prolific institution was the University Massachusetts at Amherst with 5 papers, followed by Rutgers State University with 2 papers. The most-prolific country was the USA with 7 papers, followed by Australia with 3 papers.

The papers in ‘nanotechnology applications in encapsulation of foods’, outlined in Table 27.3, relate to the development and discussion of the nanotechnology applications in food encapsulations. The most-prolific paper was a paper by Taylor et al. (2005) on the overview of liposomal nanocapsules in foods with 229 citations and 29 citations per year. Semo et al. (2007) studied the development of nanocapsules for nutraceutical delivery with 23 citations per year whilst Donsi et al. (2011), Zimet and Livney (2009), and Jafari et al. (2008) studied the nanoencapsulation of essential oils, development of nanoencapsulation of nutraceuticals, and nanoencapsulation of fish oils with 37, 22, and 19 citations per year, respectively. Augustin and Hemar (2009) and Mozafari et al. (2008) provided an overview of nanoencapsulation of food ingredients and nanoliposome applications in foods with 28 and 21 citations per year, respectively.

It is notable that all these papers, published mostly in journals related to food science and technology between 2005 and 2011, were mostly articles and the average number of citations was 204. These papers were instrumental in increasing public awareness about the nanotechnology applications in food encapsulations where the most-prolific lead author was Livney with 2 papers and most of the lead authors were male. The average number of pages per paper and number of references per paper were 11 and 57, respectively.

The papers in ‘nanotechnology applications in food packaging’, outlined in Table 27.4, relate to the development and discussion of the nanotechnology applications in food packaging with the emphasis on the development of nanobiocomposites for this purpose. The most-prolific paper was a paper by Duncan (2011) on the overview of nanotechnology applications in food packaging and food safety with 535 citations and 89 citations per year. Similarly, Sorrentino et al. (2007), Rhim et al. (2013), Jamshidian et al. (2010), De Azeredo (2009), Rhim and Ng (2007), Silvestr et al. (2011), Arora and Padua (2010), and Espitia et al. (2012) provided an overview of nanotechnology applications in food packaging with 42, 101, 51, 42, 28, 42, 30, 48 citations per year, respectively. On the other hand, Rhim et al. (2006), Avella et al. (2005), Rhim et al. (2009), and Sanpui et al. (2008) studied the preparation of nanobiocomposites for food packaging with 40, 34, 35, and 20 citations per year, respectively.

It is notable that all these papers, published mostly in journals related to food science and technology between 2005 and 2013, were mostly reviews and the average number of citations was 332. These papers were instrumental in increasing public awareness about the nanotechnology applications in food packaging where the most-prolific lead author was Rhim with 4 papers and most of the lead authors were male. The average number of pages per paper and number of references per

Table 27.3 Citation classics in nanotechnology applications in encapsulation of foods

	Author	Year	Doc.	Insts.	Country	NA	AG	Lead author	LA RA	NP	NR	Journal	Subject	Topic	Cits1	Cits2
30	Taylor et al.	2005	R	Univ. Massachusetts, Univ. Tennessee	US	4	M	Weiss, Jochen	Univ. Hohenheim	14	135	Crit. Rev. Food Sci. Nutr.	Food Sci. Technol., Nutr. Diet.	Overview of liposomal nanocapsules in foods	229	19
31	Semo et al.	2007	A	Technion Israel Inst Technol.	Israel	4	F	Livney, Yoav D	Technion Israel Inst Technol.	7	12	Food Hydrocolloids	Food Sci. Technol., Chem. Appl.	Development of nanocapsules for nutraceutical delivery	225	23
32	Donsi et al.	2011	A	Univ. Salerno	Italy	4	M	Ferrari, Giovanna F	Univ. Salerno	7	19	LWT Food Sci. Technol.	Food Sci. Technol.	Nanoencapsulation of essential oils	223	37
35	Augustin and Hemar	2009	R	CSIRO	Australia	2	F	Hemar, Yacine	Univ. Auckland	11	69	Chem. Soc. Rev.	Chem. Mult.	Overview of nanoencapsulation of food ingredients	221	28
43	Mozafari et al.	2008	R	Monash Univ.; Univ. Athens	Australia, Greece	4	M	Hatziantoniou, Sophia F	Univ. Patras	19	91	J. Liposome Res.	Bioch. Mol. Biol., Phar. Phar.	Overview of nanoliposome applications in foods	187	21
49	Zimet and Livney	2009	A	Technion Israel Inst Technol.	Israel	2	F	Livney, Yoav D	Technion Israel Inst Technol.	7	39	Food Hydrocolloids	Food Sci. Technol., Chem. Appl.	Development of nanoencapsulation of nutraceuticals	173	22
52	Jafari et al.	2008	A	Univ. Queensland, James Cook Univ. +1	Australia, Iran	4	M	Jafari, Seid Mahdi	Gorgan Univ. Agr. Sci. and Nat. Res.	12	35	Food Res. Int.	Food Sci. Technol.	Nanoencapsulation of fish oils	171	19

Doc document type, *A* article, *R* review, *NA* number of authors, *AG* author gender, *F* female, *M* male, *LA RA* lead authors' current institution, *NP* number of pages, *NR* number of references, *Subject* subject category of journals designated by the databases, *Cits1* the total number of citations received, *Cits2* the average number of citations per year

Table 27.4 Citation classics in nanotechnology applications in food packaging

	Author	Year	Doc.	Insts.	Country	NA	AG	Lead author	LA RA	NP	NR	Journal	Subject	Topic	Cits1	Cits2
2	Duncan	2011	R	US FDA	USA	1	M	Duncan, Timothy	Ill. Inst. Technol.	24	429	J. Colloid Interface Sci.	Chem. Phys.	Overview of nanotechnology applications in food packaging and food safety	535	89
4	Rhim et al.	2006	A	Mokpo Natl. Univ., Michigan State Univ. +1	S. Korea; USA	4	M	Rhim, Jong-Whan	Mokpo Natl. Univ.	9	61	J. Agric. Food Chem.	Food Sci. Technol.	Preparation of nanobiocomposites for food packaging	440	40
5	Sorrentino et al.	2007	R	Univ. Salerno	Italy	3	M	Sorrentino, Andrea	Natl. Res. Counc.	12	152	Trends Food Sci. Technol.	Food Sci. Technol.	Overview of nanobiocomposites for food packaging	419	42
6	Avella et al.	2005	A	CNR, TNO	Italy, Netherlands	6	M	Avella, Maurizio	CNR	8	14	Food Chem.	Food Sci. Technol., Chem. Appl. +1	Development of nanobiocomposites for food packaging	409	34
7	Rhim et al.	2013	R	Mokpo Natl. Univ., Michigan State Univ.	S. Korea; USA	3	M	Rhim, Jong-Whan; Ha, Chang-Sik	Mokpo Natl. Univ.; Pusan Natl. Univ.	24	221	Prog. Polym. Sci.	Polym. Sci.	Overview of nanobiocomposites for food packaging	406	101
9	Jamshidian et al.	2010	R	Inst. Natl. Polytech. Lorraine	France	5	M	Desobry, Stephane	Univ. Lorraine	20	146	Compr. Rev. Food. Sci. Food Saf.	Food Sci. Technol.	Overview of polylactic acid as nanobiocomposites for food packaging	358	51
12	de Azeredo	2009	R	Embrapa Trop. Agroind	Brazil	1	F	de Azeredo, Henriette MC F	Embrapa Trop. Agroind.	14	206	Food Res. Int.	Food Sci. Tech.	Overview of nanobiocomposites for food packaging	334	42
20	Rhim and Ng	2007	R	Mokpo Natl. Univ., Michigan State Univ.	S. Korea, USA	2	M	Rhim, Jong-Whan	Mokpo Natl. Univ.	23	211	Crit. Rev. Food Sci. Nutr.	Food Sci. Technol., Nutr. Diet.	Nanotechnology and its applications in the food sector	283	28

(continued)

Table 27.4 (continued)

	Author	Year	Doc.	Insts.	Country	NA	AG	Lead author	LA RA	NP	NR	Journal	Subject	Topic	Cits1	Cits2
23	Rhim et al.	2009	A	Mokpo Natl. Univ., Pusan Natl. Univ.	S. Korea	3	M	Rhim, Jong-Whan, Ha, Chang-Sik	Mokpo Natl. Univ.	6	24	LWT Food Sci. Technol.	Food Sci. Technol.	Determination of properties of nanobiocomposites for food packaging	279	35
27	Silvestre et al.	2011	R	CNR	Italy	3	F	Silvestre, Clara F	CNR	17	163	Prog. Polym. Sci.	Polym. Sci.	Overview of nanoapplications in food packaging	250	42
36	Arora and Padua	2010	R	Univ. Illinois, Urbana	US	2	M	Padua, Graciela W F	Univ. Ill. U. C.	7	74	J. Food Sci.	Food Sci. Technol.	Overview of nanobiocomposites for food packaging	212	30
38	Espitia et al.	2012	R	Univ. Fed. Vicosa	Brazil	6	F	Soares, Nilda de Fatima Ferreira F	Univ. Fed. Vicosa	18	91	Food Bioprocess Technol.	Food Sci. Technol.	Overview of nanoparticles for food packaging	204	41
44	Sanpui et al.	2008	A	Indian Inst. Technol.	India	5	M	Chattopadhyay, Arun	Indian Inst. Technol.	5	18	Int. J. Food Microbiol.	Food Sci. Technol., Microbiol.	Antibacterial properties of nanobiocomposites for food packaging	184	20

Doc document type, *A* article, *R* review, *NA* number of authors, *AG* author gender, *F* female, *M* male, *LA RA* lead authors' current institution, *NP* number of pages, *NR* number of references, *Subject* subject category of journals designated by the databases, *Cits1* the total number of citations received, *Cits2* the average number of citations per year

paper were 14 and 139, respectively. The most-prolific institution was the Mokpo National University of South Korea with 4 papers, followed by Michigan State University and CNR with 2 papers each. The most-prolific country was the USA with 5 papers, followed by South Korea and Italy with 4 and 3 papers, respectively.

The papers in ‘nanotechnology applications in food safety’, outlined in Table 27.5, relate to the development and discussion of the nanotechnology applications in food safety and health. The most-prolific paper was a paper by Weir et al. (2012) on the TiO_2 determination in foods and personal care products and human exposure to TiO_2 with 641 citations and 121 citations per year. Ai et al. (2009), Tiede et al. (2008), Wang et al. (2006), and Varshney and Li (2007) studied the melamine detection in milk and infant formula, detection of nanomaterials in foods and the environment, detection of polybrominated diphenyl ethers in water and milk samples, and detection of *Escherichia coli* in foods with 49, 34, 25, and 17 citations per year, respectively.

On the other hand, Bouwmeester et al. (2009) provided an overview of nanofood safety with 33 citations per year whilst Siegrist et al. (2007) studied the public acceptance of nanotechnology applications in foods with the emphasis on the food safety and health with 19 citations per year.

It is notable that all these papers, published mostly in journals not related to food science and technology due to its interdisciplinary character between 2006 and 2012, were mostly articles and the average number of citations was 313. These papers were instrumental in increasing public awareness about the nanotechnology applications in food safety and health where most of the lead authors were male. The average number of pages per paper and number of references per paper were 10 and 65, respectively. The most-prolific institution was the ETH Zurich of Switzerland with 2 papers. The most-prolific countries were the USA, Switzerland, and China with 2 papers each.

The papers in ‘other nanotechnology applications in foods’, outlined in Table 27.6, relate to the development and discussion of the nanotechnology applications in other areas with the emphasis on the biosynthesis of nanomaterials using foods. The most-prolific paper was a paper by Zhu et al. (2012) on the development of nanomaterials via soy milk with 329 citations and 55 citations per year. Philip (2009), Ankamwar et al. (2005), Dubey et al. (2010), Ruan et al. (2011), Jain et al. (2009) and Maensiri et al. (2007) studied nanoparticle biosynthesis using edible mushroom extract, nanomaterial biosynthesis using fruit extract, biosynthesis of nanomaterials using fruits, development of graphene from food, waste and insects, biosynthesis of nanomaterials using fruit extracts, biosynthesis of nanomaterials using egg white with 41, 24, 33, 37, 26, and 18 citations per year, respectively.

It is notable that all these papers, published mostly in journals not related to food science and technology due to its interdisciplinary character between 2005 and 2012, were entirely articles and the average number of citations was 255. These papers were instrumental in increasing public awareness about the nanotechnology applications in biosynthesis of nanomaterials using foods where most of the lead

Table 27.5 Citation classics in nanotechnology applications in food safety

	Author	Year	Doc.	Insts.	Country	NA	AG	Lead author	LA RA	NP	NR	Journal	Subject	Topic	Cits1	Cits2
1	Weir et al.	2012	A	Arizona State Univ.; ETH Zurich; NTNU	USA; Switzerland, Norway	5	M	Westerhoff, Paul	Arizona State Univ.	9	42	Environ. Sci. Technol.	Eng. Env., Env. Sci.	TiO_2 determination in foods and personal care products and human exposure to TiO_2	641	128
8	Ai et al.	2009	A	Chinese Acad. Sci.	China	3	M	Lu, Lehui	Univ. Chinse Acad. Sci.	3	12	J. Am. Chem. Soc.	Chem. Mult.	Melamine detection in milk and infant formula	388	49
17	Tiede et al.	2008	R	Univ. York, Univ. Gothenburg +2	England, Sweden	6	F	Tiede, Karen F	Food Env. Res. Agency	27	211	Food Addit. Contam. Part A-Chem.	Chem. Appl., Food Sci. Tech. +1	Detection of nanomaterials in foods and the environment	308	34
25	Bouwmeester et al.	2009	R	Wageningen Univ. Res. +1	Netherlands	10	M	Bouwmeester, Hans	Wageningen Univ. Res.	11	87	Regul. Toxicol. Pharmacol.	Med. Leg.; Phar. Phar.	Overview of nanofood safety	265	33
33	Wang et al.	2006	A	Nankai Univ.	China	4	M	Yan, Xiu-Ping	Nankai Univ.	7	39	J. Chromatogr. A	Bioch. Res. Meth.; Chem. Anal.	Detection of polybrominated diphenyl ethers in water and milk samples	223	25
40	Siegrist et al.	2007	A	ETH Zurich, EMPA	Switzerland	4	M	Siegrist, Michael	ETH Zurich	8	41	Appetite	Behav. Sci.; Nutr. Diet.	Public acceptance of nanotechnology applications in foods	192	19
50	Varshney and Li	2007	A	Univ. Arkansas	US	2	M	Li, Yanbin	Univ. Arkansas	7	23	Biosens. Bioelectron.	Biophys; Nanosci. Nanotechn. +2	Detection of *Escherichia coli* in foods	172	17

Doc document type, *A* article, *R* review, *NA* number of authors, *AG* author gender, *F* female, *M* male, *LA RA* lead authors' current institution, *NP* number of pages, *NR* number of references, *Subject* subject category of journals designated by the databases, *Cits1* the total number of citations received, *Cits2* the average number of citations per year

Table 27.6 Citation classics in other nanotechnology applications in foods

	Author	Year	Doc.	Insts.	Country	NA	AG	Lead author	LA RA	NP	NR	Journal	Subject	Topic	Cits1	Cits2
13	Zhu et al.	2012	A	Chinese Acad. Sci.	China	3	M	Dong, Shaojun	Chinese Acad. Sci.	3	35	Chem. Commun.	Chem. Mult.	Development of nanomaterials via soy milk	329	55
15	Philip	2009	A	Mar Ivanios Coll.	India	1	M	Philip, Daizy F	Mar Ivanios Coll.	8	40	Spectroc. Acta Pt. A-Molec. Biomolec. Spectr.	Spectr.	Nanoparticle biosynthesis using edible mushroom extract	325	41
18	Ankamwar et al.	2005	A	Natl. chem. Lab.	India	3	M	Sastry, Murali	Monash Univ.	7	61	J. Nanosci. Nanotechnol.	Chem. Appl., Nanosci. Nanotech. +3	Nanomaterial biosynthesis using fruit extract	289	24
29	Dubey et al.	2010	A	Univ. E Finland; Univ. Jyvaskyla	Finland	3	F	Dubey, Shashi Prabha F	TPS Coll. India	7	47	Process Biochem.	Biot. Appl. Microb.; Eng. Chem.	Biosynthesis of nanomaterials using fruits	232	33
34	Ruan et al.	2011	A	Rice Univ.	US	4	M	Tour, James M	Rice Univ.	7	36	ACS Nano	Chem. Mult.; Chem. Phys. +2	Development of graphene from food, waste and insects	221	37
37	Jain et al.	2009	A	Univ. Rajasthan	India	4	M	Kothari, SL	Amit Univ. Rajasthan	7	29	Dig. J. Nanomater. Biostruct.	Nanosci. Nanotech.; Mats. Sci. Mult.	Biosynthesis of nanomaterials using fruit extracts	205	26
45	Maensiri et al.	2007	A	Khon Kaen Univ.; Univ. arizona +1	Thailand, USA	4	M	Maensiri, Santi	Suranaree Univ.	4	32	Scr. Mater.	Nanosci. Nanotech., Mats. Sci. Mult. +1	Biosynthesis of nanomaterials using egg white	183	18

Doc document type, *A* article, *R* review, *NA* number of authors, *AG* author gender, *F* female, *M* male, *LA RA* lead authors' current institution, *NP* number of pages, *NR* number of references, *Subject* subject category of journals designated by the databases, *Cits1* the total number of citations received, *Cits2* the average number of citations per year

authors were male. The average number of pages per paper and number of references per paper were 6 and 40, respectively. The most-prolific country was China with 3 papers.

27.5 Authors

These citation classics were authored by 171 researchers where 12 of them had 2 or more papers. The most-prolific author was 'David Julian McClements" of University Massachusetts at Amherst of the USA with 6 papers, working on the nanotechnology applications in food emulsions. This top author was followed by 'Jong-Whan Rhim' of Mokpo National University of South Korea with 4 papers, working on the nanotechnology applications in food packaging. 'Jochen Weiss' of University Massachusetts at Amherst of the USA followed these 2 top authors with 3 papers, working mostly on the nanotechnology applications in food emulsions.

The other prolific authors were 'Mary Ann Augustin', 'Peerasak Sanguansri', and 'Tim J Wooster' of CSIRO, Australia; 'Chang-Sik Ha' of Pusan National University of South Korea; 'Qinrong Huang' of Rutgers State University of the USA; 'Yoav D Livney' of Technion Israel Institute of Technology of Israel; 'Perry KW Ng' and 'Hwan-Man Park' of Michigan State University of the USA; and 'Peerasak Sanguansri' of CSIRO.

It was found that there was a significant gender deficit among the first authors of 53 citations classics as only 12 of them were female. Similarly, 11 lead authors were female, confirming the presence of the gender deficit among the lead authors as well. This study confirms the presence of the significant gender deficit in the research related to nanotechnology applications in foods as in other scientific disciplines such as nanoscience and nanotechnology and food science and technology (Abramo et al. 2009; Jagsi et al. 2006; Probert 2005; Sax et al. 2002).

The average number of authors per paper was 3.48 suggesting that the teamwork was necessary for these papers. Fourteen, 11, and 10 papers had 4, 3, and 2 authors, respectively, where the number of authors per paper ranged from 1 to 10.

In contrast, 5340 original papers were published by 15,060 authors with the 2.8 author per paper rate on average. 'McClements DJ' was the most-prolific author publishing 2.4% of this sample. Thus, he was over-represented in the citation classics. The other most-prolific authors of the original papers were 'Zhong QX' (0.7%), 'Vicente AA' (0.6%), 'Sun QJ' (0.5%), 'Yang XQ' (0.5%), 'Huang QR' (0.5%), 'Lagaron JM' (0.5%), 'Jafari SM' (0.5%), 'Nakajima M' (0.5%), 'Kwak HS' (0.5%), 'Tan CP' (0.5%), 'Rhim JW' (0.4%), 'Martin-Belloso O' (0.4%), 'Mattoso LHC' (0.4%), 'Weiss J' (0.4%). It appears that some authors like 'Rhim JW' were over-represented in the citation classics whilst some authors like 'Zhong QX' were under-represented due to the 'first-mover advantage' bias (Kerin et al. 1992; Lieberman and Montgomery 1988, 1998).

27.6 Countries

In total, 24 countries contributed to 53 citation classics where 12 of them had 2 or more papers. The USA was the most-prolific county publishing 19 papers, 36% of the sample. Australia followed the USA with 7 papers whilst China, India, Italy, and South Korea had 4 papers each. Additionally, England had 3 papers whilst Brazil, Greece, Israel, Netherlands, and Switzerland published 2 papers each.

In contrast, China was the most-prolific country publishing 26.2% of the original sample of 5340 papers whilst the USA published only 16.2% of this sample. This finding suggests that using the 'first-mover advantage', the USA was able to produce papers with higher citations with respect to China. The late emergence of China in nanoscience and nanotechnology and in other scientific disciplines has been the focus of the research (Guan and Ma 2007; Tang and Shapira 2011; Wang et al. 2012, 2013; Zhou et al. 2013).

The other most-prolific countries were Iran, India, South Korea, Spain, Brazil, Italy, Turkey, Canada, Malaysia, England, Taiwan, Saudi Arabia publishing 11.6, 8.3, 5.6, 5, 4.7, 3.5, 3, 2.7, 2.5, 2.3, 2.1, and 2% of the original sample, respectively. The 'first-mover advantage' bias was also relevant for other countries such as Iran and India.

27.7 Institutions

In total, 75 institutions contributed to 53 citation classics where only 16 of them had 2 or more papers. The University of Massachusetts at Amherst was the most-prolific institution with 7 papers due to McClements' papers. The Commonwealth Scientific Industrial Research Organisation (CSIRO) and Mokpo National University followed this top institution with 4 papers each. Additionally, Michigan State University and Rutgers State University–New Brunswick had 3 papers each whilst Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Consiglio Nazionale delle Ricerche (CNR), ETH Zurich, Korea Food Research Institute, Pusan National University, Technion Israel Institute of Technology, University of Salerno, and University of York had 2 papers each.

In contrast, Islamic Azad University of Iran and University of Massachusetts at Amherst were the most-prolific institutions with 150 and 149 papers, respectively, in the original paper sample. The other most-prolific institutions were Jiangnan University, University of Tehran, Chinese Academy of Sciences, Consejo Superior de Investigaciones Cientificas (CSIC), South China University of Technology, United States Department of Agriculture (USDA), Council of Scientific Industrial Research (CSIR), Universiti Putra Malaysia, and King Abdulaziz University publishing 101, 83, 81, 77, 74, 70, 59, 58, and 57 original papers, respectively. Thus, it appears that institutions like Islamic Azad University, Jiangnan University, University of Tehran, South China University of Technology, and United States

Department of Agriculture (USDA) were not represented or under-represented in the citation classics sample due to the 'first-mover advantage' bias as China, Iran, and India were under-represented in the citation classics sample.

27.8 Funding Bodies

The results show that only 20 citation classics (38%) declared any source of funding and 64 funding bodies were acknowledged as a source of funding in the remaining 33 papers. The European and South Asian funding bodies dominated the list of funding bodies.

In contrast, 72.5% of the original papers declared any source of funding by 4898 funding bodies. The most-prolific funding body was National Natural Science Foundation of China funding 11.3% of the original papers' whist National Science Foundation of the USA funded only 0.6% of the original papers.

In the light of North's new institutional theory, research funding emerges as one of the most significant 'incentives' for doing research and publishing papers (Auranen and Nieminen 2010; Hicks 2012; Leydesdorff and Wagner 2009). Thus, it seems that the level of the research funding was lower for the citation classics with respect to the papers in the original sample.

27.9 Publication Years

The results show that these classical papers were published between 2005 and 2013, and the most-prolific publication years were 2008 and 2009 with 10 papers each. Thus, 64 and 36% of these papers were published in the 2000s and 2010s, respectively.

In contrast, 91.3% of the original papers were published in the 2010s whilst only 7.9% of the papers were published in the 2000s. Thus, it appears that the papers of the 2000s were over-represented in the citation classics.

27.10 Source Titles

In total, 53 citation classics were published in 35 journals where only 10 of them had 2 or more papers each. The most-prolific 3 journals related to food science and technology, Food Chemistry, Food Hydrocolloids, and Trends in Food Science Technology, had 4 papers each. Three journals again related to food science and technology, Critical Reviews in Food Science and Nutrition, Food Research International, Journal of Food Science, followed these top journals with 3 papers each. Additionally, Food Additives and Contaminants Part A Chemistry Analysis

Control Exposure Risk Assessment, LWT Food Science and Technology, and Progress in Polymer Science published 2 papers each. It is notable that 8 of these 9 top journals were related to food science and technology.

In contrast, 5340 original papers were published by 743 journals in total. The most-prolific journals were Journal of Agricultural and Food Chemistry and Food Chemistry publishing 8.4 and 8.3% of these sample papers, respectively. The other most-prolific journals were Food Hydrocolloids, LWT Food Science and Technology, Journal of Food Engineering, Food Analytical Methods, Journal of Food Science, Food Research International, Food Control, Food and Chemical Toxicology, Food and Bioprocess Technology, Trends in Food Science Technology, RSC Advances, and Talanta publishing 5.3, 3.3, 2.7, 2.5, 2, 1.9, 1.9, 1.4, 1.3, 1.1, 1.1% of the original paper sample, respectively.

Thus, it appears that all the most-prolific journals like Food Chemistry were over-represented in the citation classics whilst all the other journals like 'Journal of Food Engineering' and 'Food Analytical Methods' were under-represented or not represented at all in this sample.

27.11 Subject Categories

In total, these citation classics were indexed under 28 subject categories by the databases where only 13 of them indexed 2 or more papers each. As expected, 'Food Science and Technology' was the most-prolific subject category indexing 31 papers, 58.5% of the sample. Thus, as 41.5% of the papers were indexed by other subject categories, it is necessary to carry out the search in other subject categories as well as it was done in this study.

These other subject categories included 'Chemistry Applied', 'Nutrition Dietetics', 'Chemistry Multidisciplinary', 'Materials Science Multidisciplinary', 'Chemistry Physical', 'Nanoscience Nanotechnology' with 11, 8, 6, 5, and 5 papers, respectively. Additionally, 'Biotechnology Applied Microbiology', 'Polymer Science', and 'Toxicology' published 3 papers each whilst 'Biochemistry Molecular Biology', 'Chemistry Analytical', and 'Pharmacology Pharmacy' published 2 papers each.

27.12 Citation Impact

The citation impact of these citation classics was significant as there were 14,624 citations received for these papers in total. The average number of citations per paper was 276.23, and *h*-index was 53 meaning that 53 citing papers received 53 or more citations. There were 7876 citing papers after the citing paper sample was refined for databases (SCIE, SSCI, A and HCI), documents (article, letter, editorial material) and language (English). Articles formed 99.7% of the citing paper sample whilst editorial materials formed 0.3% of this sample.

In total, 23,529 authors authored the citing papers. The most-prolific citing author was ‘McClements DJ’ publishing 178 papers. The other prolific authors were ‘Weiss J’, ‘Rhim JW’, ‘Gao YX’, ‘Huang QR’, ‘Tan, CP’, ‘Decker EA’, ‘Nakajima M’, ‘Nasrollahzadeh M’, and ‘Lagaron JM’ publishing 59, 48, 38, 36, 36, 35, 27, 25 papers, respectively. It is notable that the most-prolific authors of the citation classics such as ‘McClements DJ’ appeared on this list as well.

In total, 104 countries were involved in publishing citing papers where only 4 countries published more than 5% of the sample each. The most-prolific country was China publishing 22% of the citing paper sample, surpassing the USA publishing only 15.1% of the sample. The other most-prolific countries were India, Iran, and South Korea publishing 12.1, 6.5, and 5.3% of the sample, respectively. The other prolific countries were Spain, Italy, Brazil, France, Germany, England, Malaysia, Canada, Saudi Arabia, Australia, and Japan publishing more than 2% each.

In total, 4283 institutions contributed to citing papers where 8 of them published more than 100 papers each. The most-prolific institution was University of Massachusetts Amherst publishing 2.8% of the sample, closely followed by Chinese Academy of Sciences publishing 2.7% of the sample. The other prolific institutions were Centre National de la Recherche Scientifique (CNRS), Consejo Superior de Investigaciones Cientificas (CSIC), Indian Institute of Technology, Islamic Azad University, Council of Scientific Industrial Research (CSIR), Universiti Putra Malaysia, King Abdulaziz University, and South China University of Technology publishing more than 1% of the sample each.

The results show that 77% of the citing papers declared a source of funding, funded by 7516 funding bodies. The most-prolific funding body was National Natural Science Foundation of China, funding 10.2% of the citing papers. In contrast, National Science Foundation and European Union funded only 0.7 and 0.6% of the citing papers, respectively.

As the citation’s classics were published between 2015 and 2013, the citing papers were published in recent years between 2006 and 2018 where 96.1% of the citing papers were published in the 2010s. The most-prolific publication year was 2017 with 1298 papers forming 16.5% of the citing paper sample, followed by 2016, 2015, 2014, and 2013 where 15.6, 15.4, 12.8, and 10.1% of the sample were published, respectively. It is notable that 8.8% of the citing paper sample was published in 2018 as of June 2018.

In total, the citing papers were published in 1016 journals. The most-prolific journal was Food Hydrocolloids publishing 3.6% of the citing papers. The other most-prolific journals were RSC Advances, Carbohydrate Polymers, Food Chemistry, Journal of Agricultural and Food Chemistry, Journal of Applied Polymer Science, LWT Food Science and Technology, Journal of Food Engineering, Food Research International, International Journal of Biological Macromolecules, Journal of Colloid and Interface Science, Colloids and Surfaces B Biointerfaces, Journal of Food Science, and Langmuir publishing 2.8, 2.8, 2.6, 2.2, 1.7, 1.6, 1.5, 1.5, 1.5, 1.2, 1.2, 1, and 1% of the sample, respectively. It is notable that a half of these top journals were related to food science and technology.

The citing papers were indexed by 153 subject categories in total. The most-prolific subject category as expected was Food Science and Technology indexing 2001 papers forming 25.4% of the siting paper sample. The other most-prolific subject categories were Chemistry Applied, Materials Science Multidisciplinary, Polymer Science, Chemistry Multidisciplinary, Chemistry Physical, Nanoscience Nanotechnology, Chemistry Analytical, Engineering Chemical, Physics Applied indexing 15.2, 13.9, 13.5, 12.6, 11.5, 10.2, 7.6, 6.6, 5.4% of the citing paper sample, respectively. Thus, these citation classics contributed to the scientific literature at large.

27.13 Conclusion

Both the food science and technology and nanoscience and nanotechnology have been a basic component of the scientific literature with over one million indexed papers each since 1980s. In the meantime, scientometrics has emerged as a new interdisciplinary scientific discipline since 1960s. This scientometric tool has been applied both to nanoscience and nanotechnology and to food science and technology. However, there has been no application of the scientometric tool to the nanotechnology applications in foods in general, although there have been 2 studies focusing on food nanopreservation and nanoemulsions used in the food industry.

This study applied the scientometric tool to the nanotechnology applications in foods in general focusing on 53 citation classics forming the top 1% of the indexed papers published in this novel research field as a first-ever study for the food science and technology. The results showed that the reviews were over-represented in these classical papers. The most-prolific subjects were ‘nanotechnology applications in food emulsions’ and ‘nanotechnology applications in food packaging’ with 13 papers each. These 2 top subjects were followed by ‘nanotechnology applications in encapsulation of foods’, ‘nanotechnology applications in food safety’, and ‘other nanotechnology applications in foods’ with 7 papers each. Additionally, there were 6 papers in nanotechnology applications in foods in general.

It is notable that these citation classics focused on the structure–processing–property relationships as in other scientific disciplines such as nanoscience and nanotechnology, food science and technology, and materials science and engineering. The most-prolific author was ‘David Julian McClements’ of University Massachusetts at Amherst of the USA with 6 papers, and there was a significant gender deficit among authors. The USA was the most-prolific county publishing 19 papers, 36% of the sample. The University of Massachusetts at Amherst was the most-prolific institution with 7 papers. Only 20 citation classics (38%) declared any source of funding and 64 funding bodies were acknowledged as a source of funding in the remaining 33 papers.

These classical papers were published between 2005 and 2013, and the most-prolific publication years were 2008 and 2009 with 10 papers each. The most-prolific 3 journals related to food science and technology, Food Chemistry, Food Hydrocolloids, and Trends in Food Science Technology had 4 papers each. As expected, 'Food Science and Technology' was the most-prolific subject category indexing 31 papers, 58.5% of the sample. The citation impact of these citation classics was significant as there were 14,624 citations received for these papers in total. The average number of citations per paper was 276.23, and *h*-index was 53. Thus, these citation classics contributed to the scientific literature at large.

The results show that the scientometric tool has a great capacity to provide timely and detailed information about 53 citation classics forming the top 1% of the original sample of 5340 papers in line with the teaching of the new institutional theory for the key stakeholders. It is recommended that a complementary study should be undertaken to apply the scientometric tool to the study of the original sample of 5340 papers. It is further recommended that the scientometric tool should be applied separately to the major topical areas such as 'nanotechnology applications in food emulsions', 'nanotechnology applications in food packaging', 'nanotechnology applications in encapsulation of foods', 'nanotechnology applications in food safety' for the more detailed coverage of these topical areas.

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