Chapter 4
Potential of Biogenic Plant-Mediated Iron and Iron Oxide Nanoparticles and Their Utility

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4.1 Introduction

Nanotechnology is manipulation of matter to produce nanomaterials with distinctive properties. A nanoparticle (NP) is a microscopic particle with a minimum of one dimension less than 100 nm in size. They have unique mechanical, optical, thermal, electrical, chemical, and physical properties, which differ from those of bulk materials, and they have a variety of applications in the domains of health care, agriculture, environmental science, energy, information technology, mass communication, heavy industry, consumer goods, biosensor development, nanobiosensor development, biomedicine development, nanobiotechnology, bionanotechnology, diagnostic drugs, therapeutic drug delivery, development of treatments/cures for various infectious and noninfectious diseases and neurodegenerative disorders, drug

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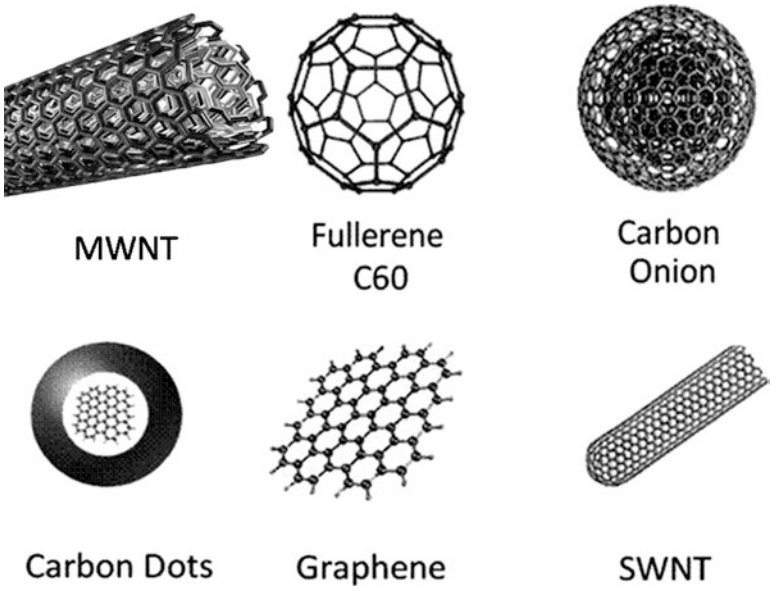

Fig. 4.1 Examples of nanomaterials

delivery using medical diagnostic tools, and cancer treatment agents (specifically, Au nanoparticles, Cu nanoparticles, Fe nanoparticles, etc.) (Singh and Choi 2010; Singh et al. 2010, 2012a, b, c, d, 2014) (Fig. 4.1).

Iron is employed in support railings and as structural beams in cars or buildings. It is also present in water, in blood to move chemical elements, and in magnets. Iron rust is iron oxide, formed from a combination of iron and oxygen. Nanoparticles of both iron and iron oxide are very useful. They are also magnetic in nature. Iron has four odd electrons, whereas the iron chemical compound has only two odd electrons. Fe^0 is black in color, whereas iron oxide is dark brown. In everyday life we are exposed to traces of iron nanoparticles or iron oxide nanoparticles (IONs), and in these trace concentrations they are nontoxic. Both types of iron are present in the environment. IONs are employed in the medical domain, e.g., as contrast agents in magnetic resonance imaging (MRI) or to improve delivery of drug treatments for neoplasms. Biological synthesis of nanoparticles can be a very challenging task and is also known as green synthesis.

Plant-mediated nanoparticle formation provides a lot of biocompatible nanoparticles in comparison with chemical synthesis of nanoparticles, and their application in the medical field can be attributed to the presence of non-toxic chemical species on the surfaces of the nanoparticles. Plant-mediated biological synthesis of nanoparticles has gained importance in recent years. With use of plants and concentrations of phytochemicals, nanoparticles can be synthesized within minutes or hours. IONs have numerous potential applications, and this has encouraged researchers to utilize them in cancer treatment, drug delivery, MRI, wastewater treatment, heat transfer

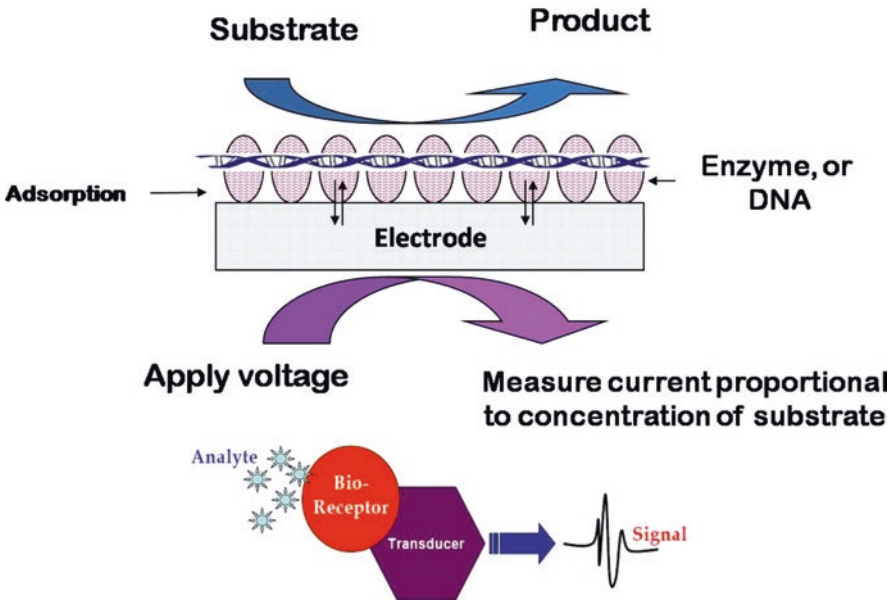

Fig. 4.2 Principle of biosensors

systems as super-robust materials, sensors, biosensors, nanosensors, nanobiosensors, antimicrobial agents, germicidal agents, catalysts, and photocatalysts (Singh et al. 2011; Shukla et al. 2010; Prasad 2014; Singh 2017, 2019) (Fig. 4.2).

Recent prospects in nanobiotechnology have increased utilization of nanomaterials, which could ultimately increase not just their benefits but also their biohazards to health and the environment. In this context, the goal is to develop environmentally benign methods for synthesis of metal and metal oxide nanoparticles to reduce their negative impacts in physicochemical ways. A green technology approach (i.e., a biological approach to synthesis of nanoparticles) has emerged and appears to be eco-friendly and efficient, being economical for very large-scale production of nanoparticles that are very valuable for use in health care, environmental, biotechnological, agricultural, and medical applications (Table 4.1).

Nanoparticles are particles with at least one dimension measuring 1–100 nm. Their properties are chiefly size dependent, with a high surface charge related to their high surface-to-volume ratio, and they have unique thermal, catalytic, optical, electrical, and magnetic properties with the potential for wide use in biological or medical applications such as treatment of metastatic tumors and antimicrobial, mosquitocidal, antiplasmodial, ovicidal, and larvicidal potential for use in the treatment of protozoal infections and infectious disease (Darezereshki et al. 2010; Shameli et al. 2012; Benelli 2016; Benelli et al. 2016; Dinesh et al. 2015; Prasad et al. 2016; Govindarajan and Benelli 2017; Vincent et al. 2017; Govindarajan et al. 2016; Murugan et al. 2015). Cancer is an international health issue. Surgery, chemotherapy, radiation, and immunotherapy are the most common regimens used

Table 4.1 Nanomaterials used in food products and packaging

Nanomaterials	Applications (in use)
Titanium nitride	Improvement of thermal properties, antimicrobial and deodorant agents, ultraviolet light filters, polyethylene terephthalate, refrigerators
Carbon black	Additives, rubbers, silicones, printing inks
Silicon dioxide	Antislipping agents, printing inks, paper and board, rubbers, silicones
Aluminum	Filler in polymers, scratch- and abrasion-resistant coatings, improvement of barrier properties, ultraviolet light filters
Silver	Antimicrobial, antibiotic, and antistatic agents; reusable food containers
Nanoclay	Improvement of barrier properties
Zinc oxide	Ultraviolet light filters, antimicrobial and fungistatic agents, deodorants, plastic glasses, plastic films

for treatment of cancer. They kill not only cancer cells but also normal cells (Tan et al. 2011; Kuppusamy et al. 2016).

Physicochemical methods for synthesis of IONs—such as sol–gel reactions, sonochemical methods, hydrothermal methods, microemulsion methods, flow injection synthesis, radiolysis, microwave methods, aerosol pyrolysis, and laser pyrolysis—have been established (Bagheri et al. 2013; Abdullah et al. 2017; Vijayakumar et al. 2000; Giri et al. 2005; Vidal-Vidal et al. 2006; Salazar-Alvarez et al. 2006; Abedini et al. 2014; Carenza et al. 2014; Tartaj et al. 2004; Bomati-Miguel et al. 2008). Nanoparticles synthesized by physicochemical methods not only lose their reactivity as a result of aggregation of air exposure, magnetism, and dispersibility but also cause contamination due to toxic solvents, by-products, and chemical precursors (Kim et al. 2008; Wu et al. 2008; Thakkar et al. 2010a).

In view of the aforementioned shortcomings, there is a growing trend toward use of clean, simple, inexpensive, and environmentally friendly approaches for synthesis of metal/metal oxide nanoparticles, using bacteria, fungi, algae, and plant extracts (Prasad et al. 2016, 2018). Plant-mediated nanoparticles are less expensive and simpler, less time consuming, much easier, and safer to use (Prasad 2014). Plant-mediated synthesis of nanoparticles is a green method for synthesis of iron and IONs, using aqueous plant extracts. Basavegowda et al. (2014a) reported green fabrication of ferromagnetic Fe_3O_4 nanoparticles and their novel catalytic application for synthesis of biologically interesting benzoxazinone and benzothioxazinone derivatives, using a fruit extract of *Artemisia annua*. Basavegowda et al. (2014b) reported use of sonochemically synthesized ferromagnetic Fe_3O_4 nanoparticles as a recyclable catalyst for preparation of pyrrolo[3,4-c]quinoline-1,3-dione derivatives, using a leaf extract of *Perilla frutescens*. Venkateswarlu et al. (2013) reported biogenic synthesis of Fe_3O_4 magnetic nanoparticles (MNPs) using a peel extract of plantain. Yew et al. (2016) reported green synthesis of magnetite (Fe_3O_4) nanoparticles using an extract of the seaweed *Kappaphycus alvarezii*.

Different parts of the *Juglans regia* tree—such as its kernels, leaves, tree bark, and green fruit husks—have been utilized in both the pharmaceutical industry and the cosmetic industry (Izadiyan et al. 2017; Stampar et al. 2006). Carvalho et al.

(2010) demonstrated antioxidant and antimicrobial activities of walnut leaves, seeds, and green husks, with use of low-cost natural materials to develop the same applications. Flavonoids, flavones, isoflavones, isothiocyanates, carotenoids, and polyphenols are also known natural resources for synthesis of metallic nanoparticles. Flavonoids have been identified to be responsible for the reduction of metal salts to synthesize IONs, along with polyhydroxy groups in santin, tannins, and saponins acting as capping agents. The presence of phenols, alkaloids, saponins, cardiac glycosides, steroids, carbohydrate, and proteins in plants has been reported to be responsible for reduction of ferric ions into nanoforms. Phenolic compounds, tannins, and alkaloids have been used for formation and stabilization of synthesized nanoparticles (Thakkar et al. 2010b).

This chapter describes synthesis of IONs with and without use of plant extracts to determine the role of these extract compounds in size control. Chang et al. (2012) reported preparation and characterization of a Fe_3O_4/graphene nanocomposite and investigation of its adsorption performance for aniline and p-chloroaniline. Chourpa et al. (2005) reported molecular composition of IONs for use as precursors for magnetic drug targeting, as characterized by confocal Raman microspectroscopy. Garcıa-Jimeno and Estelrich (2013) described a ferrofluid based on polyethylene glycol (PEG)–coated IONs, with its characterization and properties. Gholoobi et al. (2017) reported biopolymer-mediated synthesis of Fe_3O_4 nanoparticles and investigation of their in vitro cytotoxicity effects. Gupta and Gupta (2005) reported synthesis and surface engineering of IONs for biomedical applications. Hribernik et al. (2012) reported synthesis of magnetic iron oxide particles and development of an in situ coating procedure for fibrous materials. Karaoglu et al. (2011) reported synthesis and characterization of a dl-thioctic acid (DLTA)–Fe_3O_4 nanocomposite. Pardoe et al. (2003) reported an MRI-based method for measurement of tissue iron concentrations in liver arterially embolized with ferromagnetic particles designed for magnetic hyperthermia treatment of tumors. Shameli (2013) reported synthesis of talc/Fe_3O_4 magnetic nanocomposites using a chemical coprecipitation method. Zhao et al. (2010) reported magnetic and inductive heating properties of Fe_3O_4/PEG composite nanoparticles with a core–shell structure. Latha and Gowri (2014) reported ION synthesis using leaf extracts of *Carica papaya* and showed plate-like structures with coarsened grains and uniformly distributed small spherical particles. Senthil and Ramesh (2012) reported that carbohydrates containing *Tridax procumbens* plant extract were responsible for Fe_3O_4 nanoparticle synthesis at room temperature, and also revealed the presence of alkaloids, carotenoids, flavonoids, saponins, and tannins, reported to be responsible for the Fe_3O_4 nanoparticle synthesis.

Synthesis of metal and metal oxide nanoparticles by biological methods may lead to development of clean, environmentally acceptable, and nontoxic nanoparticles. Biosynthesis of safe and easily distributed IONs uses plant extracts with single and mixed iron salts.

4.2 Contrast Agents for Magnetic Resonance Imaging

MNPs are used as contrast agents for MRI because they have superparamagnetic properties, which permit them to be magnetized only under the influence of an externally applied magnetic flux, and to lose this magnetization once the field is deactivated. This property permits superparamagnetic IONs (SPIONs) to be employed in MRI as negative contrast agents. The pharmacokinetic properties of SPIONs permit them to accumulate, in a very nonspecific manner, in the mononucleate somatic cell system, which facilitates their use in MRI of organs such as the liver and spleen, lymph nodes, and bone marrow (Josephson et al. 1988; Park et al. 2009; Wang 2011; Hemmingsson et al. 1987; Weissleder et al. 1990; Seneterre et al. 1991). Arami et al. (2015) reported use of IONs either as effective bioimaging contrast agents or as carriers of biomolecules such as drugs, nucleic acids, and peptides for controlled delivery to specific organs and tissues. They noted that many vital criteria (e.g., size and size distribution, charge, coating molecules, and plasma supermolecule adsorption) may be effectively tuned to regulate the in vivo pharmacokinetics and biodistribution of the iron oxides. Skaat et al. (2013) described antibody-conjugated, dual-modal, near-infrared fluorescent IONs for antiamyloidgenic activity and specific detection of amyloid-β (Aβ) fibrils. The Aβ peptide is the main fibrillar component of plaque deposits found in brains affected by Alzheimer disease (AD) and is related to the pathogenesis of AD.

In a critical review, Ferguson et al. (2013) reported that magnetic particle imaging (MPI) is a promising new modality for imaging the distribution of ION tracers in vivo with high contrast, high sensitivity, and smart spatial resolution for clinical imaging in angiography and oncology. Ittrich et al. (2013) reported the use of SPIONs to image physiological processes and anatomical, cellular, and molecular changes in disease. The clinical applications range from imaging of tumors and metastases in the liver, spleen, and bone marrow to imaging of lymph nodes and the central nervous system (CNS), magnetic resonance angiography (MRA), perfusion imaging of atherosclerotic plaques, and thrombosis imaging. The authors described new experimental approaches in molecular imaging, using undirected superparamagnetic iron oxide (SPIO) trapping (passive targeting) in inflammation, tumors, and associated macrophages with directed accumulation of SPIO ligands (active targeting) in tumor endothelia and tumor cells, areas of programmed cell death, infarction, inflammation, and degeneration in cardiovascular and neurological diseases, and in atherosclerotic plaques or thrombi. They additionally reported the labeling of stem or immune cells to permit visualization of cell therapies or transplant rejection. Further, they reported coupling of SPIOs to ligands, radiotherapeutics, and/or chemotherapeutics, embedding in carrier systems or activatable smart device probes, and externally controlled focusing (physical targeting) to modify molecular tumor therapies or to image metabolic and catalyst processes. Finally, they speculated that monodispersed SPIOs with defined physicochemical and pharmacodynamic properties will improve SPIO-based MRI in the future, and use of SPIONs as targeted probes in diagnostic magnetic resonance (DMR) using chip-based micronuclear magnetic resonance (μNMR)

may considerably expand the spectrum of in vitro analysis strategies for biomarkers, pathogens, and tumor cells.

As a brand new imaging modality, MPI offers new applications for SPIOs in cardiovascular, oncological, cellular, and molecular diagnostics and medical care. Bellusci et al. (2014) studied SPIONs as candidate contrast agents for MRI and targeted drug delivery. They stated that biodistribution and toxicity assessments are essential for the development of nanoparticle-based drugs, owing to nanoparticle-enhanced biological reactivity, and they investigated the in vitro and in vivo potential toxicity of metallic element solid solution ($MnFe_2O_4$) nanoparticles, using cultures of murine Balb/3T3 fibroblasts. Park et al. (2014) reported the effects of PEG molecular weight on the stability, T_2 contrast, cytotoxicity, and cellular uptake of SPIONs. The monodispersed SPIONs were synthesized and coated with PEG of variable molecular weights. They showed adequate stability and magnetic contrast, and exhibited minimal cytotoxicity and nonspecific cellular uptake. This work provided insights into the potential for safe clinical application of SPIONs.

The current research on SPIONs is opening up wide horizons for their use as diagnostic agents in resonance imaging and as drug delivery vehicles. Delivery of malignant neoplasm treatments to their target sites by coupling with functionalized SPIONs is one of the foremost areas of research in the development of cancer treatment strategies. In addition, SPIONs have incontestable potency as nonviral cistron vectors, which facilitate the introduction of plasmids into the nucleus at rates many times those of commonly available normal technologies. SPION-induced hyperthermia has additionally been utilized for localized killing of cancerous cells. Despite their potential medical specialty applications, alterations in gene expression profiles, disturbances in iron homeostasis, oxidative stress, and altered cellular responses are SPION-related toxicity aspects that need to be considered. A comprehensive understanding of SPIONs with regard to their preparation techniques, their utility as drug delivery vehicles, and a few other considerations is required before they can move from the benchtop to the bedside. Wahajuddin and Arora (2012) reported use of SPIONs as a magnetic nanoplatform for a targeted drug delivery system. SPIONs are small, synthetic γ-Fe_2O_3 (maghemite) or magnetic iron ore particles with a core ranging between 10 nm and 100 nm in diameter.

These magnetic particles are coated with certain biocompatible polymers, such as dextran or PEG, which provide chemical handles for conjugation of therapeutic agents and additionally improve the blood distribution profile. Tsuchiya et al. (2011) reported a histological study of the biodynamics of iron chemical compound nanoparticles with totally different diameters. Kucheryavy et al. (2013) reported synthesis of magnetic iron ore nanoparticles within a size range of 3.2–7.5 nm and in high yields under variable reaction conditions, using high-temperature hydrolysis of precursor iron(II) and iron(III) alkoxides in a diethylene glycol solution. The average sizes of the particles were adjusted by varying the reaction temperature and time, and by employing a consecutive growth technique. To obtain γ-iron(III) oxide particles within the same range of sizes, magnetite particles were oxidized with dry oxygen in diethylene glycol at room temperature. This resulted in an improved prospective imaging agent thanks to its chemical stability. Dadashzadeh et al. (2013)

reported that labeling of cells with SPIONs provided the flexibility to trace cells by MRI. Quantifying intracellular iron concentrations in SPIO-tagged cells would allow comparison of agents and techniques used to magnetically label cells. Kut et al. (2012) assessed the potential for injury to normal tissues in mice due to heating of systemically delivered MNPs in an alternating magnetic flux (AMF).

MNPs with even a modest heat output will cause harm, and even death, when sequestered in adequate concentrations. Dextran–SPIONs are deposited in the liver and spleen, making these sites of potential toxicity. Sun et al. (2012) reported in vitro labeling of endothelial progenitor cells (EPCs) isolated from peripheral blood with SPIONs. Transplantation of EPCs provides a completely unique methodology for treatment of human tumors or vascular diseases. MRI has been established to be effective in following transplanted stem cells through labeling of the cells with SPIONs. Rabbit peripheral blood EPCs were effectively labeled with home-synthesized SPIONs, with no influence on their main biological characteristics.

Kim et al. (2013) reported cerebral blood volume (CBV) MRI with intravascular SPIONs. The CBV could be a crucial physiological indicator of tissue viability and vascular reactivity. CBV-weighted functional MRI (fMRI) with ultrasmall SPIONs (USPIONs) provides increased sensitivity, a reduced large-vessel contribution, and improved spatial specificity relative to standard blood oxygenation level–dependent fMRI, and measures a single physiological parameter that is easily interpretable.

Toki et al. (2013) described a comprehensive analysis of transfection-assisted delivery of IONs to nerve fiber cells, with elaborated data on toxicity and the potency of polylysine (PL)–facilitated uptake of USPIONs by nerve fiber cells for cell-specific MRI. PL has been used to facilitate nerve fiber cell uptake of SPIONs to be used in MRI. The data suggested that utilization of PL to boost the labeling of dendritic cells (DCs) with SPIONs could be worthwhile. Acceptable standardization of the incubation time and concentrations of PL and SPIONs is crucial for the development of MRI technology for noninvasive imaging of DCs in vivo.

Starmans et al. (2013) reported ION micelles for sensitive (molecular) MPI and MRI. IONs are a promising nanoplatform for contrast-enhanced MRI as a brand new imaging modality that is able to directly visualize magnetic particles and provides a sensitive and quantitative alternative to MRI. The FibPep-ION-Micelle platform provides in vivo, noninvasive imaging of fibrin in diagnostic models of thrombus-related pathologies and coronary artery disease.

Schweiger et al. (2012) reported quantification of the internalization patterns of SPIONs with opposite charges. Shevtsov et al. (2014) reported a study of SPIONs conjugated with recombinant human epidermal growth factor (EGF) as a possible agent for MRI contrast enhancement for malignant brain tumors, using a C6 brain tumor cell culture. SPION–EGF conjugates offer targeted delivery and economical magnetic resonance contrast improvement of EGF receptor (EGFR)–overexpressing C6 gliomas.

Wei et al. (2012) reported use of compact zwitterion-coated IONs for biological applications. The potential of SPIONs in various medical specialty applications, together with MRI, sensing, and drug delivery, requires that their surface be derivatized

to be hydrophilic and biocompatible. The authors reported synthesis of a compact and water-soluble zwitterionic dopamine sulfonate (ZDS) ligand with sturdy binding affinity for SPIONs. Simberg et al. (2009) reported a differential genetic analysis of the surface heterogeneity of dextran–IONs and also the implications for their in vivo clearance.

These data offer possibilities for a rational type of bioinert, long-circulating nanoparticles. Uchiyama et al. (2015) evaluated the use of cationic USPIONs as a nontoxic and economical MRI contrast agent and magnetic targeting tool. Cationic USPIONs provide a useful platform for the recent development of new materials for applications in theranostics.

Zaloga et al. (2015) reported that different storage conditions influence the biocompatibility and physicochemical properties of IONs. Their effectiveness of this therapy is dependent on the magnetic properties, stability, and biocompatibility of the particles. Ziv-Polat et al. (2012) described novel magnetic fibrin hydrogel scaffolds containing thrombin and growth factors conjugated with IONs for tissue engineering. Tomitaka et al. (2015) reported use of lactoferrin-conjugated IONs for targeting brain tumor cells in MPI. MPI could be a new real-time imaging modality, guaranteeing high tracer mass sensitivity and spatial resolution directly generated from IONs. Chao et al. (2012) reported recognition of dextran–SPION conjugates (Feridex) via macrophage scavenger receptor charged domains. Dextran-coated SPIONs (dextran–SPION conjugates) offer the chance to enhance MRI imaging sensitivity so that small or diffuse lesions can be detected. Juang et al. (2013) reported MRI of mouse islet grafts labeled with novel chitosan-coated SPIONs. They found that after syngeneic and allogeneic transplantation, islets labeled with these nanoparticles could be effectively and safely imaged by MRI. Gamarra et al. (2010) described use of MRI for quantification of SPIONs in biological materials. Ren et al. (2011) reported facile, high-potency immobilization of lipase enzyme on magnetic IONs via a biomimetic coating. Immobilization of lipase on suitable solid supports is a method to boost stability and activity, and may be reused for very large-scale applications.

The quest for a simple, cost-effective, and high-loading-capability technique continues to be challenging. Immobilization of enzymes onto magnetic IONs via polydopamine film is economical. Kolhatkar et al. (2015) reported primary in vitro enzymatic synthesis of paramagnetic and magnetic nanoparticles for magnetic enzyme-linked immunosorbent serological assay coverage. Enzymatic synthesis of magnetic labels reduced costs and avoided the diffusional mass transfer limitations associated with presynthesized magnetic reporter particles, while retaining the benefits of magnetic sensing.

Magnetic IONs are renowned for their applications in MRI, hyperthermia, targeted drug delivery, etc. Surface modification of those MNPs has been explored extensively to realize functionalized materials with potential applications in medicine, environmental science, and catalysis. Bhandari et al. (2016) reported a unique and versatile single-step methodology for developing curcumin-functionalized magnetic Fe_3O_4 nanoparticles with no further linkers, employing a straightforward coprecipitation technique. The MNPs were characterized using transmission

microscopy, x-ray diffraction, Fourier transform infrared (FTIR) spectroscopy, and thermogravimetric analysis. The developed MNPs were utilized in a cellular application for protection against an inflammatory agent—a polychlorinated biphenyl (PCB) molecule. Beckers et al. (2013) reported improved effects of nanometer-sized metallic (Pd, Ag, and Cu) and metallic oxide (Fe_xO_y) nanoparticles, encapsulated in porous silicon dioxide, on fermentative biohydrogen production from glucose by *Clostridium butyricum* bacteria. They observed an improvement in electron transfer through combinations of enzymatic activity and inorganic materials. Granot and Shapiro (2011) reported release activation of IONs (REACTION)—a completely unique, environmentally sensitive MRI paradigm.

Smart contrast agents for MRI-based cell tracking would enable utilization of MRI methodologies to detect not just the location of cells but also gene expression. Muller et al. (2008) studied the effect of atorvastatin on uptake of USPIONs (ferumoxtran-10) in human monocyte macrophages and its implications for MRI. Ferumoxtran-10 is beneficial as a contrast material in MRI for diagnosis of inflammatory and degenerative disorders related to high scavenger cell activity. Atanasijevic et al. (2006) described use of calcium-sensitive MRI contrast agents based on SPIONs and calmodulin.

Roh et al. (2006) reported extracellular synthesis of magnetic iron ore and metal-substituted magnetite nanoparticles. They developed a novel microbial method that exploited the ability of Fe(III)-reducing microorganisms to supply copious amounts of extracellular magnetites and metal-substituted magnetite nanoparticles. The Fe(III)-reducing microorganisms (*Theroanaerobacter ethanolicus* and *Shewanella* sp.) had the ability to reduce Fe(III) and various metals in aqueous media and formed various-sized magnetic iron ore and metal-substituted magnetite nanocrystals. The Fe(III)-reducing microorganisms formed the metal-substituted magnetites using iron oxide and other metals (e.g., Co, Cr, Mn, and Ni) in conditions of a comparatively low temperature (<70 °C), ambient pressure, and neutral to slightly basic hydrogen ion concentrations (pH 6.5–9). Baumgartner et al. (2016) reported elongated magnetite nanoparticle formation from a solid metallic element precursor in a very magnetotactic microorganism. Magnetotactic microorganisms are aquatic microorganisms that intracellularly mineralize ferrimagnetic nanoparticles, enabling the cells to align with the geomagnetic field. The microorganisms produce a magnetic mineral of a species-specific phase (magnetite $Fe(II)Fe(III)_2O_4$ or greigite $Fe(II)Fe(III)_2S_4$), size, morphology, and particle assembly. The authors investigated the formation of such irregularly shaped nanomagnets in the species *Desulfovibrio magneticus* RS-1. Their findings represented a completely unique observation on the interconversion of iron (oxyhydr)oxide materials, and they recommended that solid-state growth processes might be needed to supply irregularly shaped, elongated magnetic iron ore nanocrystals.

Cheng and Hsu (2017) used a facile technique to organize SPIO- and hydrophobic drug–encapsulated perishable polyurethane nanoparticles for use in a variety of medical applications such as MRI, targeting, and hyperthermia therapy. Norouz Dizaji et al. (2016) described an environmentally friendly procedure for silver (Ag) or gold (Au) deposition onto magnetic iron ore nanoparticles, using plant extracts

(*Ligustrum vulgare*) as reducing and stabilizing agents. The magnetic iron ore nanoparticles (measuring ~6 nm) with superparamagnetic properties were synthesized by coprecipitation of Fe^{2+} and Fe^{3+} ions. Color changes indicated differing amounts of Au and conductor ions reduced and deposited onto the SPIONs when the plant extracts were used. Magnetic saturation decreased when the quantity of the metallic deposition was magnified, which was measured by vibrating-sample magnetometry (VSM). The Ag/Au–deposited SPIONs were stable, and virtually no agglomeration was discovered for months. The Ag/Au–carrying magnetite nanoparticles originated from the plant extracts.

Wang et al. (2016) reported in vitro assessment of physiological changes in watermelon (*Citrullus lanatus*) growth with exposure to IONs. Nanobased iron fertilizer is used in agricultural applications. The authors reported that γ-Fe_2O_3 nanoparticles seemed to display an intrinsic peroxidase-like activity and had the power to improve iron deficiency chlorosis and promote the expansion of the watermelon plants.

4.3 Wastewater Treatment

Water is a universal solvent and is essential for life on earth. Two thirds of the earth's surface is covered by water, and 97% of the world's water is found in the oceans. Only 2.5% of the world's water is nonsaline H_2O, 75% of which is bound up in glaciers and ice caps; the remaining 25% of it is found in lakes, ponds, and rivers. Water is an essential resource for living systems, industry, agriculture, and domestic use. An adequate supply of safe water is a prerequisite for a healthy life.

Pollution occurs when a product added to the natural environment adversely affects nature's ability to dispose of it. Waste products adversely interfere with the health, comfort, property, and life style of individuals. Most pollutants are introduced into the environment as biodegradable pollution, agricultural waste, domestic waste, industrial waste, accidental discharges, and compounds used for plant and animal protection. As a result of the increasing demand for water and the shortage of its supply, it is necessary to intensify the development of water resources in the world and to ensure that water is used efficiently by appropriate treatment and management of this resource (Itodo and Itodo 2010).

A brand new quaternary magnetic Fe_3O_4/ZnO/Ag_3VO_4/AgI nanocomposite has been developed and was shown to be an excellent visible-light-driven photocatalyst, fabricated via preparation of a Fe_3O_4/ZnO/Ag_3VO_4 nanocomposite followed by coupling of it with silver iodide through ultrasonic irradiation. The magnetic properties of the nanocomposite offered a convenient way to separate the photocatalyst from the reaction mixture by use of an external magnet (Aziz and Gohari 2016).

Iron nanoparticles obtained from tea leaf extract have been shown to contain iron compounds and oxohydroxide. Shahwan et al. (2011) reported green synthesis of iron nanoparticles and the effectiveness of their application as a Fenton-like catalyst

for removal of aqueous cationic and anionic dyes, such as methylene blue and methyl orange, over a large range of concentrations (10–200 mg L^{-1}).

Chromium is used in a variety of industries and plays specific roles in refractories, alloy production, electroplating, pigment production, catalyst generation, and animal skin tanning. It is found in the environment as trivalent and hexavalent ions. Trivalent chromium is employed as a necessary macronutrient for the regulation of lipid, supermolecule, and protein metabolism; however, excessive concentrations may cause toxicity due to disturbances of red blood cell membranes and may also cause skin irritation. Hexavalent chromium is even more toxic. It can penetrate the skin and kill cells, and it can damage polymers through generation of reactive oxygen species (ROS). The World Health Organization (WHO) has reported that chromium is genotoxic and is recognized as an individual group 1 carcinogen. Widespread ecosystem exposure to chromium poses an environmental threat; thus, removal of Cr(VI) from the environment is probably necessary. Remediation of soil, water, etc., to remove chromium is an urgent requirement.

The utility of nanoparticles for remediation of hexavalent chromium species has been demonstrated (Guertin et al. 2016; Mishra and Bharagava 2016; Owlad et al. 2009). Keller et al. (2012) reported toxicity of three commercial forms (uncoated, with an organic coating, and with an iron oxide coating) of nanoscale zero-valent iron (nZVI) to freshwater and marine organisms—specifically, three species of marine phytoplankton, one species of freshwater plant, and a freshwater zooplankton species (*Daphnia magna*). These organisms could be exposed downstream of wherever nZVI is applied to remediate contaminated soil. Zhu et al. (2008) reported uptake, translocation, and accumulation of factory-made IONs by pumpkin plants (*Cucurbita maxima*) grown in a liquid medium containing iron ore (Fe_3O_4) nanoparticles. Duan et al. (2014) described use of hierarchical hybrid peroxidase catalysts for remediation of phenol wastewater. Zhang et al. (2014) reported a straightforward solvothermal method for fabrication of a metal–organic framework with an iron oxide enclosure for determination of organophosphorus pesticides in biological samples. Cheng et al. (2015) reported removal of pentachlorophenol (PCP) from water with use of nZVI as a heterogeneous Fenton catalyst in an nZVI/H_2O_2 system; nZVI is an environmentally benign material and has been widely used as a reducing agent in treatment of environmental pollutants. The initial H_2O_2 concentration considerably influenced the phencyclidine removal rate, and nZVI performed better than commercial zero-valent iron (ZVI) as a catalyst. Moreover, iron ore (Fe_3O_4), which was the most abundant product of corrosion of the nZVI, was found to perform well as an adsorbent and catalyst; thus, it allowed the nZVI to be effectively reused. Wu et al. (2009) reported utilization of Fe^0 nanocomposites stabilized with extremely reactive iron ore (Fe_3O_4) nanoparticles for reduction and mitigation of hexavalent chromium(VI) species in liquid solutions. Zhou et al. (2016) reported utilization of Fe/Ni bimetallic particles to remove Cr(VI) from an aqueous solution in an ultrasound-assisted system across a pH range of 3–9.

Synthesis of iron nanoparticles through reduction of iron salt precursors with plant extracts has been widely established. What is more challenging is finding ways to control their properties—specifically, their size, shape, reactivity, monodispersity,

oxidation potential, crystallinity, etc. (Valle et al. 2017). Wang et al. (2014) synthesized iron nanoparticles with green tea and eucalyptus leaves, which were able to remove nitrate. Luo et al. (2016) showed that grape leaf–mediated synthesis of Fe/Pd bimetallic nanoparticles removed orange II dye from a solution. Martinez-Cabanas et al. (2016) used eucalyptus-generated iron nanoparticles encapsulated in a chitosan matrix for removal of As(V) in column flow-through experiments.

Liu et al. (2008) evaluated oxidation of IONs, using humic acid and carbon as coating materials, for economical removal of heavy metals in water. Herrera-Becerra et al. (2007) reported that plant biomass not only provided an ample supply of carbon to coat as-synthesized nanoparticles with or without pretreatment but also served as a reducing agent when the hydrogen ion concentration was controlled. The hydrogen ion concentration was a size-limiting parameter. Ramasahayam et al. (2012) developed a protocol for microwave-assisted synthesis of a magnetic nanocomposite, using pinewood shavings and a spacer (saturated NaCl), and oven drying without microwaving and use of a spacer. Tannin played an important role in the production of reduced iron oxide using pinewood shavings and a spacer, while plastic materials were also used to synthesize and stabilize metal nanoparticles with oven drying without microwaving and use of a spacer. The reduced iron oxide nanocomposite size resulting from use of this protocol was used to remove phosphorus from water.

Lopez-Tellez et al. (2013) described use of ethanol-treated orange peel powder to synthesize iron oxide nanorods. The cellulose content of the orange peel functioned as a reducing agent for the metal ions, and the nanoparticles that were formed were stabilized on the surface of the orange peel by electrostatic and weak van der Waals interactions between the reduced form of the metal and the functional groups of the cellulose and hemicellulose components. The researchers found that iron was deposited on the surface of the biomass in the forms of iron, iron(II) oxide, and iron ore, and it was shown that this nanobiocomposite removed chromium from sewer water. Lunge et al. (2014) reported synthesis of inexpensive iron ore nanoparticles, using tea waste as a template, and identified a cuboid/pyramid-shaped crystal structure of magnetite nanoparticles with a size range of 5–25 nm. Additionally, they used as-synthesized nanoparticles for removal of arsenic (As(III) and As(V)) and demonstrated higher adsorption capability.

The use of IONs in medicine and environmental remediation has led to considerations concerning exposure of the general public to those nanoparticles. Few studies are available to gauge their effects on the environment, particularly on plants and food crops. Bombin et al. (2015) described the biological processes and reproductive effects of IONs in *Arabidopsis thaliana*. They investigated the consequences of positively charged (PC) and negatively charged (NC) Fe_2O_3 IONs on the physiology and reproductive capability of cress plants at concentrations of 3 and 25 mg/L. The plants treated with the 3-mg/L concentration failed to show evident effects on seeding and root length. The treated plants failed to show any discernible phenotypical changes in overall size or general natural characteristics, indicating that environmental nanoparticle contamination may be dangerously underestimated.

In agriculture, pesticides have became one of the key environmental pollutants. Fe_3O_4 IONs coated with catalysts, enzymes, or maybe even antibodies could be used as biosensors. Ali et al. (2013) described a potentiometric urea biosensor utilizing a chitosan–magnetic ION nanobiocomposite. Chauhan et al. (2016) prepared a nanobiocomposite from Fe_3O_4 and poly(indole-5-carboxylic acid) for detection of pesticides such as malathion and chlorpyrifos in a large range of concentrations (0.1–70 nm). Iron nanoparticles in the elemental state have additionally been utilized for purification of water and tested against reductive dehalogenation of organochlorine pesticides and insecticides, and chromium and arsenic. Modification of agglomeration of iron nanoparticles by use of surfactants not only reduces organochlorine pesticides but also prevents corrosion (Wang and Zhang 1997; Lien and Zhang 2001; Zhang 2003; Hu et al. 2004; Kanel et al. 2006). Mukherjee et al. (2015) reported utilization of ZVI particles made from steel industry waste for in situ remediation of groundwater contaminated with the organochlorine pesticide heptachlor.

Pesticides utilized in agriculture are somewhat harmful to animals and plants, and use of IONs for their removal could be very useful. Keum and Li (2004) reported reduction of nitroaromatic pesticides with ZVI and recommended its use for remediation, but this would release unhealthy residues into the environment.

4.4 Sensors/Biosensors/Nanosensors/Nanobiosensors

There are current trends and challenges associated with use of smart nanomaterials for various applications that pertain to biosensor development, engineering science, and nanobiotechnology. These growth areas can have a motivating influence on the manifestation of the latest ultrabiosensing devices (nanobiosensors) to resolve severe pollution issues in the future, which not only pose threats to human health but will also have adverse effects on other living entities (Singh 2016). These sensors could have various applications in the clinical, environmental, and agricultural fields (Prasad et al. 2014, 2017). Their ability to sense chemicals and biological agents that are present in air, foodstuffs, and water could be of interest. They will pioneer the ways in which the quality of air, food, and water is measured, because of their size and the speed and accuracy of their measurements (Fig. 4.3).

Top-down lithography, bottom-up assembly, and molecular self-assembly are the main strategies for producing nanosensors. These include chemical nanosensors (detecting very tiny amounts of chemical vapors), nanobiosensors (for cancer detection), nanoscale electrometers, deployable nanosensors, and multianalyte sensing element arrays (e.g., for chemical monitoring and disease detection). The particulars of the nanostructures (e.g., their size) and also the materials being used are essential in developing nanosensors such as nanoscale wires (with the capability for extreme detection sensitivity), carbon nanotubes (with very large surface areas), thin films, and nanoparticles.

The main advantage of nanosensors lies in their extraordinarily high surface-to-volume ratios, which permit high sensitivity and detection of as little as one molecule

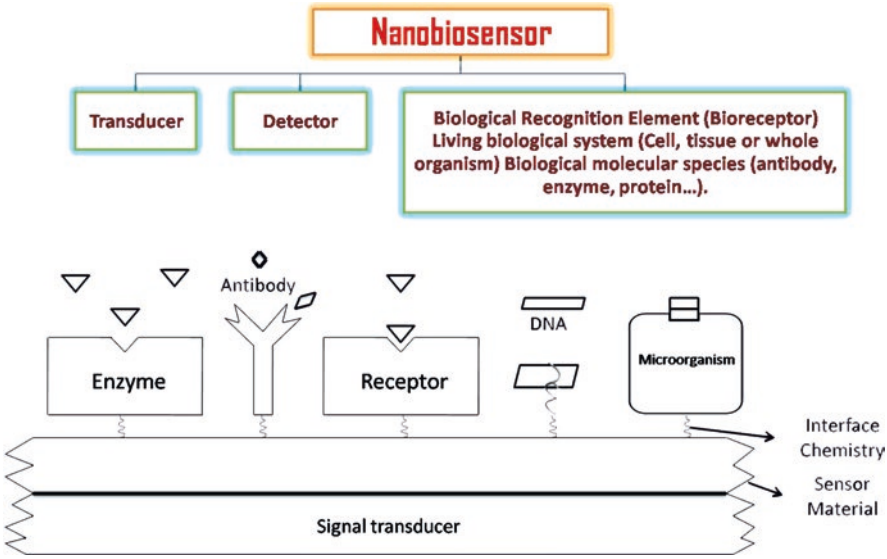

Fig. 4.3 Principle of nanobiosensors

or atom. MNPs have good potential for magnetic hyperthermia treatment, drug delivery, and cell sorting (Hilger et al. 2002; Li et al. 2015; Kocbek et al. 2013). Paramagnetic IONs can be used as contrast agents in MRI and photothermal therapy for cancer. Fe_3O_4 MNPs can be used for liver imaging, as a contrast agent for MRI, in immunochemical assays, for biosensing, and for drug delivery. Silica-coated iron oxide PEG-coated nanoparticles with a contrast component of gadolinium (Gd) have been used to access a particular area of the brain to find a neoplasm (Marcus et al. 2016; Yoo et al. 2008; Yu et al. 2008; Kamat et al. 2010, Singh 2016). IONs exhibit good biocompatibility and are regarded as stable. IONs labeled with antibodies can be used to detect carcinoma cells in vitro. Additionally, IONs conjugated with luteinizing hormone–releasing carcinoma cells can be used to find carcinoma in vivo (Artemov et al. 2003).

Karlsson et al. (2008) reported that copper oxide nanoparticles were extremely toxic in a comparison between metal oxide nanoparticles and carbon nanotubes. The manufacture and use of nanoparticles are increasing; humans are exposed to them occupationally or via merchandise and also via the environment. Different metal oxide (CuO, TiO_2, ZnO, $CuZnFe_2O_4$, Fe_3O_4, and Fe_2O_3) nanoparticles and nanotubes have been investigated and compared with regard to their cytotoxicity and ability to cause DNA injury and oxidative stress. Their toxicity was compared with that of carbon nanoparticles and multiwalled carbon nanotubes (MWCNTs), using the human respiratory organ epithelial cell line A549, which was exposed to the particles, and the cytotoxicity was analyzed using trypan blue staining. DNA injury and oxidative lesions were determined using a comet assay, and intracellular production of ROS was measured using the oxidation-sensitive fluoroprobe 2,7-dichlorofluorescin diacetate (DCFH-DA).

Shanmugam et al. (2011) reported an analysis of a sensitive, fast-response, enzymatic nanointerfaced biosensor for detection of putrescine. Putrescine (1,4-diaminobutane) is a biologically active diamine and a valuable analyte for clinical and analytical use. The enzyme diamine oxidase (DAO) was immobilized on IONs to quantify the amount of putrescine created by decarboxylation of ornithine, which was converted into hydrogen peroxide by the DAO. Rossi et al. (2004) reported an aldohexose oxidase–magnetite nanoparticle bioconjugate for glucose sensing. Immobilization of bioactive molecules on the surface of MNPs is done to enhance the delivery and recovery of biomolecules in medical specialty applications. The authors described the preparation and functionalization of magnetic iron-ore (Fe_3O_4) nanoparticles 20 nm in diameter and also the successful covalent conjugation of the enzyme glucose oxidase to the amino-modified nanoparticle surface. Functionalization of the MNP surface with amino groups greatly increased the amount and activity of the immobilized enzyme in comparison with immobilization procedures involving physical adsorption. Immobilization of glucose oxidase on the nanoparticles also improved the stability of the enzyme. Almeida et al. (2017) reported carbon disulfide–mediated self-assembly of laccase and IONs on gold surfaces for biosensing applications.

4.5 Antimicrobial/Bactericidal Agents

It has been speculated that application of a sufficient external magnetic flux to IONs can be used to destroy microorganism membranes. The germicidal effects of metal nanoparticles may additionally be attributed to their small size and high surface-to-volume ratio. Many synthetic antibiotics available on the market have the major disadvantage of multiple resistance of detrimental microorganisms to individual drugs. Recent developments and opportunities to explore the germicidal effects of metal nanoparticles could resolve this problem. It has been established that antibacterial activity increases with a decrease in nanoparticle size and is also related to its form and orientation. Therefore, the concentration of nanoparticles is a significant issue for antibacterial activity. Lee et al. (1996) reported that inactivation of *Escherichia coli* by ZVI nanoparticles could be due to penetration of its cell membranes by these tiny particles (ranging in size from 10 to 80 nm) and their reaction with intracellular oxygen—i.e., oxidative stress—which causes disruption of the semipermeable membrane. Lee et al. (1996) reported germicidal effects of ZVI nanoparticles on *E. coli*.

Utilization of plant extracts for synthesis of iron nanoparticles has been studied to identify plants with high inhibitor concentrations and different phytochemical compositions that can be used in antimicrobial and/or medical applications. It has been established that soluble phytochemical extracts derived from plants can be used to form iron salt precursors into iron nanoparticles with antimicrobial and medical properties (Vuong et al. 2014). Davenport et al. (2000) reported that iron nanoparticles were oxidized to FeO and Fe_2O_3, with a film being formed on the surface of the nanoparticles, which prevented corrosion of the deeper layer.

SPIONs are frequently used in magnetic drug targeting, MRI, tissue repair, etc. When a chelating agent such as PO_4^{3-} is used in an air-saturated system, the biocidal activity of iron nanoparticles is reduced as a result of Fe(III) forming an insoluble metal chelate with PO_4^{3-} particles, whereas once a salt ($C_2O_4^{2-}$) particle is used, the germicidal activity is increased as a result of it forming a soluble complex with the iron particle. This is often additionally shown and monitored by a change in color from black to yellow. Fe(II) is very prone to oxidation by air; it does not remain stable unless it is stabilized by an acid.

SPIONs are helpful in drug delivery because an external magnetic flux can be used to direct them to the desired target and keep them there until the magnetic flux is brought to a halt. The size and form of Fe_3O_4 nanoparticles can also be controlled by monitoring the hydrogen ion concentration, the temperature, and the concentration of the reacting elements. Coating with an appropriate wetting agent will forestall their agglomeration (Hafeli et al. 1997; Lian et al. 2004; Zaitsev et al. 1999; Kang et al. 1996; Wang et al. 2013).

Whereas the deformation of the cell increases with the concentration of SPIONs. Coating of nanoparticles additionally influences the toxicity of the nanoparticles. Dextran-coated SPIONs are approved by the US Food and Drug Administration (FDA). The toxicity of empty SPIONs and SPIONs coated with –COOH and $–NH_2$ has been evaluated using the human cell lines HCM (heart), BE-2C (brain), and 293 T (kidney). The toxicity of the empty SPIONs was found to be greater than that of those coated with organic molecules because of their greater affinity to soak up proteins, vitamins, amino acids, and ions, changing the hydrogen ion concentrations of the drugs. Since the human cell contains proteins, vitamins, and amino acids, affinity is needed for binding with SPIONs, whereas SPIONs already coated with these substances have no empty space for chelation with them. The toxicity of coated SPIONs is therefore lower than that of uncoated ones. The low toxicity of coated SPION is beneficial for detection of cancer cells; as a result, they do not harm normal cells. One variety of SPION is detrimental to bound sorts of cells, whereas other varieties have insignificant effects (Mahmoudi et al. 2009a, b, c; Mahmoudi et al. 2010). Arakha et al. (2015) described antimicrobial activity of IONs upon modulation of the nanoparticle–bacterium interface. Chitosan coating of IONs leads to an interface that enhances ROS production and hence their antimicrobial activity.

Metal oxide and gold nanoparticles represent a brand new category of vital materials that are progressively being developed for use in analysis and health-related activities. In view of the immense importance of the biological system, elemental understanding of the influence of inorganic nanoparticles on cellular growth and functions is vital. Chatterjee et al. (2011) reported the effects of iron oxide and gold nanoparticles on microorganism growth, with a view to biological applications. The Fe_3O_4 and Au nanoparticles were prepared and characterized, and it was found that the IONs inhibited *E. coli* in an exceedingly concentration-dependent manner, whereas the gold nanoparticles showed no such activity. The authors additionally noted a metal nanoparticle–bacterium interaction at the cellular level, which could be utilized for useful biological applications; however, it additionally poses the potential for ecotoxicity, challenging the eco-friendly nature of nanoparticles.

4.6 Cancer/Tumor Therapy

The most commonly used MNPs are primary solid-solution nanoparticles or IONs, which have potential uses in drug and gene delivery, particular medical specialties, and novel fields such as theranostic nanomedicine. In essence, three completely different approaches are often utilized in the treatment of tumors with SPIONs: magnetically evoked hyperthermia, drug targeting, and selective suppression of neoplasm growth (Yu and Sun 2010). Also, tumor identification is often greatly improved as a result of the capability of MNPs to supply far better contrast in MRI, significantly increasing its sensitivity (Li et al. 2013).

Another promising technique that is improved by the properties of SPIONs is MPI, which has extremely high temporal resolution with high acquisition rates, achieving much greater sensitivity than MRI (Weizenecker et al. 2009). Khan et al. (2012) studied exposure of cancer cells to iron compound nanoparticles and observed that. They noted that these nanoparticles could be safely utilized in the treatment of tumors without damaging healthy cells. Additionally, they examined ROS generation when A549 cancer cells were treated with IONs, which subsequently induced autophagy. Wu et al. (2011a) reported selective growth inhibition of oral cancer by iron core–gold shell nanoparticles through mitochondria–mediated autophagy and showed that the gold-coated iron nanoparticles suppressed neoplastic cell growth in oral and colorectal cancer cells in vivo and in vitro. Healthy cells were equally exposed to the iron nanoparticles but were not greatly affected; also, the replication of cancer cells was repressed. Toxicity was possible because of the magnetic properties of the nanoparticles; however, their oxidation was reduced by the gold coating. ROS scavengers did not defend cancer cells from nanoparticles with Fe@Au-induced toxicity. The oxidation of iron nanoparticles and generation of ROS were coincidental processes that caused consecutive autophagy and suppressed neoplastic cell growth (Wu et al. 2011b).

Nanoparticles that are geared toward targeting of cancer cells but spare healthy tissues offer an attractive platform of implementation for hyperthermia or as carriers of chemotherapeutics. Pottler et al. (2015) reported genotoxicity of SPIONs in granulosa cells. They demonstrated that use of different coatings on the SPIONs improved their biocompatibility, particularly in terms of genotoxicity to cells of the genital system. Cai et al. (2010) published the first report of synthesis of Fe_3O_4 SPIONs with a size of 8 nm at an ambient temperature and normal air pressure, using soybean sprouts as a biotemplate. The biotemplate served as the nucleation site and controlled the dimensions and morphology of the nanoparticles on the cuticular surface and the interior stem wall when the biotemplate was immersed in Fe^{2+} and Fe^{3+} solutions for 4 hours and treated with NaOH. The nanoparticles that were recovered from the biotemplate were precipitated using processes of milling, magnetic separation, washing, and drying. The nanoparticle formation was confirmed by FTIR analysis, and a possible role of soybean sprout proteins and other biomolecules in nanoparticle synthesis was demonstrated.

MPI permits high spatial resolution and sensitivity, and also offers the chance to create real-time images by determining the spatial distribution of magnetic particles. To assess a prospective biosafe application of University of Luebeck dextran-coated (UL-D) superparamagnetic nanoparticles, the biocompatibility of SPIONs, their impact on biological properties, and their cellular uptake were evaluated by Lindemann et al. (2014), using head and neck squamous cancer cells (HNSCCs). The concluded that UL-D SPIONs are a promising tracer material for use in innovative neoplasm cell analysis by MPI. Hoff et al. (2013) reported a comparative study of ferrofluid and powder ION permeation through the blood–brain barrier. They found that the ferrofluid formulations achieved statistically greater permeation than the ION powder formulations at the barrier, suggesting potential uses for in situ–synthesized ferrofluid formulations of polyvinyl alcohol, bovine albumen, collagen, glutaminic acid, graphene, and their mixtures as materials that could cross the barrier to deliver medicine or achieve other neurological therapeutic efficacy. The results showed that a formulation of IONs with collagen achieved the least permeation across the barrier, suggesting that this could be used as an MRI contrast agent while limiting ION passage across the blood–brain barrier.

Shen et al. (2012) reported that IONs attenuated antigen-specific humoral responses and T lymphocyte cytokine expression in ovalbumin-sensitized mice. They found that one dose of IONs attenuated delayed-type hypersensitivity (DTH) reactions by suppressing infiltration and activity of T helper 1 cells and macrophages in response to antigen stimulation.

The presence of multidrug resistance-associated protein (MRP) in cancer cells is understood to be responsible for various therapeutic failures in current oncological treatments. Franke et al. (2013) reported that exposure of cancer cells to different physiological condition, IONs, and mitomycin C influences membrane MRP expression levels. This concept could be used to develop new treatment options using inhibitory mechanisms that actively export drugs from the target cells, thereby improving therapeutic outcomes in oncology. Daldrup-Link et al. (2011) described use of MRI in tumor-associated macrophages with clinically applicable IONs. The growth improvement achieved with clinically applicable IONs could offer a brand new biomarker for long-term prognosis, relevant treatment choices, and thus analysis of new immune-targeted therapies. Sharma et al. (2014) reported that ION agglomeration influences dose rates and modulates oxidative stress–mediated dose–response profiles in vitro. Namvar et al. (2014) reported cytotoxic effects of magnetic IONs synthesized using a seaweed aqueous extract. The synthesis of Fe_3O_4 MNPs involved reduction of a ferric chloride solution, using a brown seaweed (*Sargassum muticum*) aqueous extract containing hydroxyl radicals, carboxyl, and amino functional groups mainly relevant to polysaccharides, which could act as a possible stabilizer and metal reductant agent, with multiple applications across a broad spectrum of medical specialties, together with identification and treatment of cancer. The researchers evaluated the in vitro cytotoxic activity and cellular effects of Fe_3O_4 MNPs in human cell lines for cancer of the blood (Jurkat cells), breast cancer (MCF-7 cells), cervical cancer (HeLa cells), and cancer of the liver (HepG2 cells).

The nature of the synthesis and therapeutic potential of Fe_3O_4 MNPs could pave the way for additional analysis on green synthesis of therapeutic agents, notably in nanomedicine, to help with cancer treatment. Jingting et al. (2011) reported preparation and characterization of MNPs containing Fe_3O_4–dextran–anti-β-human chorionic gonadotropin (a new-generation choriocarcinoma-specific gene vector) by chemical coprecipitation and confirmed that Fe_3O_4–dextran–anti-β-human chorionic gonadotropin nanoparticles have potential as a secure, effective, and choriocarcinoma-specific cistron vector. Wu et al. (2014) reviewed nanoiron metal and nanoiron oxides, which are among the most widely used engineered and naturally occurring nanostructures. The increasing incidence of biological exposure to those nanostructures has therefore raised concerns regarding their biotoxicity due to ROS-induced oxidative stress, which depends upon the chemical composition, particle size, and crystalline phase of the particles; the physiological pH range; biogenic reducing agents; and different organic substances.

Lee et al. (2013) studied theranostic nanoparticles with controlled release of gemcitabine for targeted medical care and MRI in pancreatic cancer. The tumor stroma in human cancers considerably limits the delivery of therapeutic agents into cancer cells. To develop a good therapeutic approach that would overcome the physical barrier of the stroma, the researchers engineered urokinase plasminogen activator receptor (uPAR)–targeted magnetic IONs carrying the chemotherapy drug gemcitabine (Gem) for targeted delivery into uPAR-expressing growth and stromal cells. They concluded that theranostic amino terminal fragment (ATF)–ION–Gem nanoparticles have good potential in the development of targeted therapeutic and imaging approaches that are capable of overcoming the tumor stromal barrier to enhance the therapeutic effects of nanoparticle drugs on pancreatic cancers. Wang and Cuschieri (2013) described tumor cell labeling by MNPs with determination of the intracellular iron content and the spatial distribution of the intracellular irons. Magnetically labeled cells are used for in vivo cell tracking by MRI in clinical translation of cell-base therapies. Dextran-coated SPIO ferumoxides are used clinically as contrast agents primarily for internal organ imaging. This material is also widely used for in vitro cell labeling, as are different SPIO-based particles. Findings on the uptake of ferumoxides by human neoplastic cell lines indicate that electroporation in the presence of protamine sulfate (PS) leads to rapid and high uptake of SPIONs by parenchymal growth cells without important impairment of cell viability, thus ensuring the potential of this system for clinical tumor cell detection and destruction. Hanini et al. (2011) reported an evaluation of the biocompatibility of polyol-produced maghemite γ-Fe_2O_3 nanoparticles and confirmed that they caused necrobiosis within 24 hours of exposure, possibly through oxidative stress, and led to toxicity in the liver, kidneys, and lungs but not in the brain or heart.

Since γ-Fe_2O_3 may exhibit harmful properties, surface coating, cellular targeting, and local exposure need to be considered before developing clinical applications are developed. Malvindi et al. (2014) described a toxicity assessment of silica/silicon oxide/silicon dioxide/oxide–coated IONs and biocompatibility improvement by surface engineering using A549 and HeLa cells. They used empty and surface-passivated Fe_3O_4/SiO_2 nanoparticles to gauge the effects of coating on the particle

stability and toxicity. The results indicated that surface engineering of Fe_3O_4/SiO_2 nanoparticles played a key role in increasing particle stability in biological environments, reducing cytotoxic and genotoxic effects. Williams et al. (2013) reported application of flux hyperthermia and SPIONs to HIV-1-specific T cell cytotoxicity.

Theranostic nanoparticle-supported SPIOs hold excellent promise for tumor identification and gene therapy. Li et al. (2014) reported theranostic nanoparticles based on a bioreducible polyethylenimine-coated iron oxide for redox-triggered gene release and use in MRI. They demonstrated the utility of disulfide-containing cationic polymer–decorated SPIONs as an extremely potent and low-toxicity theranostic nanosystem for specific nucleic acid delivery within cancer cells. West et al. (2014) reported assessment and optimization of electroporation-assisted tumoral nanoparticle uptake in a mouse model of exocrine gland ductal adenocarcinoma. Pancreatic ductal adenocarcinoma (PDAC) is usually fatal. The authors assessed the in vitro and in vivo uptake of doxorubicin-loaded iron chemical compound nanoparticles as an function of the electroporation voltage and the timing of administration in pancreatic adenocarcinoma cells. They showed that addition of electroporation to administration of nanoparticles considerably increased ION uptake by a PANC-1 cell line in an athymic mouse model of PDAC. Zhang et al. (2015) described iron nanoparticles as promising biomedical agents requiring evaluation of nanotoxicity to ensure safe application.

Schutz et al. (2014) reported differential stress reactions of human colon cells to oleic acid–stabilized and nonstabilized ultrasmall IONs, since engineered therapeutic nanoparticles, including USPIONs, can accumulate in the lower alimentary canal following intake or injection. The reactions of human colon cells to USPIONs, nonstabilized USPIONs, oleic acid–stabilized USPIONs, and free oleic acid were compared in human HT29 and Caco-2 animal colon cancer cells. The stress responses of the cells were ascertained, together with markers of programmed cell death and DNA repair, oxidative stress and degradative/autophagic stress, induction of heat shock protein, and lipid metabolism. Barhoumi and Dewez described the toxic effects of SPIONs on the green alga *Chlorella vulgaris*. Ma et al. (2012) reported that intraperitoneal injection of magnetic Fe_3O_4 nanoparticles induced hepatic and renal tissue injury via oxidative stress in mice.

Because of their distinctive magnetic properties, Fe_3O_4 nanoparticles have been widely used, and their applications in numerous fields have promised major benefits. Horniblow et al. (2015) studied alginate–iron speciation and its effects on in vitro cellular iron metabolism. Alginates are a category of biopolymers with known iron-binding properties. Additionally, alginates influence iron absorption in humans. They are beneficial for chelation of excess iron, particularly in the context of inflammatory bowel disease and colorectal cancer, where excess unabsorbed luminal iron is believed to be a driver of disease. Alili et al. (2015) reported an effect of Fe_3O_4 nanoparticles on neoplasm cells and dermal fibroblasts. They examined the toxicity, production of ROS, and invasive capability during treatment of human dermal fibroblasts (HDFs) and cells from the squamous tumor cell line SCL-1 with Fe_3O_4 nanoparticles. Tseng et al. (2015) studied use of cetuximab (cet)–conjugated IONs for cancer imaging and medical care. They developed theranostic nanoparticles—cet-PEG-dexSPIONs—by conjugation of the anti-EGFR antibody cetuximab

to dextran-coated SPIONs via periodate oxidation. They demonstrated that use of cet-PEG-dexSPIONs maintained the therapeutic effects of cetuximab in addition to offering a way to focus on and image EGFR-expressing tumors. Cet-PEG-dexSPIONs represent a promising targeted magnetic probe for early detection and treatment of EGFR-expressing tumor cells.

Foy and Labhasetwar (2011) reported that IONs facilitated cancer diagnosis through enhanced contrast, selective enhancement of tumor necrobiosis with magnetic hyperthermia, and improved drug delivery with magnetic drug targeting. They proposed that high doses of IONs can be used as a treatment for cancer by generating an oxidative assault against the cancer. This proposal might be met with resistance, considering the controversy regarding iron in the field of cancer. Iron generates ROS through the Fenton reaction, which can either cause or cure cancer; thus, iron deprivation or iron overdose could be potential cancer therapies. Sungsuwan et al. (2015) reported lipopeptide-coated IONs as potential glycoconjugate-based synthetic anticancer vaccines. Zhu et al. (2010) reported oxidative stress and programmed cell death induced by IONs in cultured human umbilical endothelial cells. Shen et al. (2015) reported core–shell structured Fe_3O_4@ TiO_2–doxorubicin nanoparticles for targeted chemosonodynamic cancer treatment. The engineered nanoparticles were endowed with multiple functions permitting them to selectively deliver a combination therapy payload to the tumor with increased therapeutic effectiveness and minimal side effects. Zhang et al. (2016) reported that dietary IONs delayed aging and ameliorated neurodegeneration in a *Drosophila melanogaster* AD model. IONs can mimic catalase and may decompose ROS. This has potential uses in the treatment of aging, metabolic disorders, and neurodegenerative diseases in which increased production of ROS may occur.

4.7 Drug Delivery

SPIONs have important applications in drug delivery. The drugs are bound on the SPION surface or encapsulated in magnetic liposomes and microspheres—which may deliver peptides, DNA, chemotherapeutics, and radioactive and hyperthermic medicines—and are targeted to the required site using an external magnetic flux. This method can allow reductions in the drug dose, absorption time, and interaction with nontarget cells. The iron nanoparticles need to be magnetic and smaller than the target cells so they can simply diffuse into them. Since use of a large abundance of SPIONs can result in agglomeration, high concentrations of them could also be avoided. Guo et al. (2009) described use of monodisperse mesoporous superparamagnetic single-crystal magnetite nanoparticles for drug delivery of doxorubicin, and ascertained that these nanoparticles had a very high drug-loading capability and slow release. Butoescu et al. (2009) performed an efficacy study in which magnetically retainable microparticles were used for drug delivery to a joint in an antigen-induced inflammatory disease model in mice.

Drug release is controlled by porousness, temperature, sensitivity, pH, surface functionalization, and biodegradability of the nanoparticles. Zhang et al. (2002) reported surface modification of superparamagnetic magnetite nanoparticles to improve their intracellular uptake for drug delivery to a desired target without interaction with other living cells. In the case of breast cancer (BT20 cells), PEG-coated nanoparticles between 10 and 100 nm in size were found to penetrate the cells. It is believed that since PEG is relatively soluble in both polar and nonpolar solvents, it can release the MNPs into neoplasm cells.

Magnetic IONs are an excellent drug carrier utilized in chemotherapy and are selective for cancer cells. Wang et al. (2008) described use of a variety of bimetallic nanoparticles of the kind MFe_2O_4 (where M = bivalent Mg, Fe, Co, Ni, Cu, or Zn) containing two metal ions for medical specialty applications. Multifunctional MNPs can be prepared by coating them with gold, silica, zinc oxide, polymer, liposomes, etc., and can be additionally functionalized to make the MNPs stable and multifunctional. Xu and Sun (2013) reported new kinds of superparamagnetic nanoparticles for medical specialty applications such as delivery of cisplatin to a solid tumor, using Fe_3O_4 HMNPs. It was shown that the drug could be delivered via matter exchange.

To extend the target yield of SPIONs, they are typically coated with polymers and functionalized by attaching carboxyl groups, biotin, avidin, carbodiimide, or other biomolecules. Koneracka et al. (1999) reported immobilization of proteins and enzymes, using fine magnetic particles. Mehta et al. (1997) reported direct binding of protein to magnetic particles, and Koneracka et al. (2002) reported direct binding of proteins and enzymes to fine magnetic particles. Alexiou et al. (2000) reported that once the drug is carried to the target cell (tumor cell), it can be discharged either by application of an external magnetic force or by changes in the pH, force per unit area, or temperature. Widder et al. (1978) reported that the drug is then taken up by the neoplasm cells and penetrates them via diffusion.

SPIONs are stable at a neutral hydrogen ion concentration, and the stability of the colloidal suspension relies on the dimensions and form of the nanoparticles and whether aggregation occurs; this can be prevented by coating them with an applicable surface-active agent. Tartaj and Serna (2003) reported synthesis of monodisperse superparamagnetic Fe/silica nanospherical composites. Barratt et al. (2002) reported that larger particles (larger than 10 nm) cannot penetrate the endothelium under normal conditions, whereas Moghimi et al. (2001) reported that they can easily penetrate tumor cells and inflamed cells. Gupta et al. (2007) described recent advances in surface engineering of magnetic IONs and medical specialty applications for them. Once coated nanoparticles enter tumor cells, the coating is dissolved in the biological fluid and they are exposed to other cellular elements. Hong et al. (2007) compared different methods for preparing magnetic Fe_3O_4 nanoparticles. Once the concentration is raised, aggregation of nanoparticles can occur, resulting in a larger magnetic interaction, and it was suggested that agglomeration of nanoparticles in capillaries could block their passage. Douziech-Eyrolles et al. (2007) described nanovectors for antitumor agents, using SPIONs at a biological hydrogen

ion concentration and therefore a SPION isoelectric point at a hydrogen ion concentration of 7.0 for colloidal stability of the SPIONs.

When normal cells are exposed to drug delivery, it is essential that the drug is nontoxic to them. Thomsen et al. (2013) reported uptake and transport of SPIONs through human brain capillary endothelial cells. Sun et al. (2013) described use of synthesized aminosilane-coated IONs (AmS-IONs) to construct complex and multifunctional drug delivery systems. They determined the impacts of the surface charge and magnetic flux on the toxicity and uptake of AmS-IONs in CNS-relevant cell types, i.e., a mouse brain microvessel endothelial cell line (bEnd.3) and cultivated mouse astrocytes and neurons. They found that the toxicity seemed to depend on the surface coating rather than on the number of IONs present in the cell. Mistry et al. (2014) reported that nitrite induces extravasation of IONs in hypoxic tumor tissue. Nitrate undergoes reconversion to nitric oxide under conditions that are characteristic of the tumor microenvironment, such as hypoxia and a low hydrogen ion concentration. This selective conversion of nitrite into nitric oxide in tumor tissue provides an opportunity to improve drug delivery and therefore the radiation response. Dani et al. (2014) reported the use of a temperature-tunable ION-based delivery system for remotely controlled drug release specifically aimed at cancer cells. This delivery system showed good potential for remotely triggered drug delivery and therefore destruction of cancer cells. Prosen et al. (2013) described magnetofection—a reproducible technique for gene delivery to malignant melanoma cells—as a nanoparticle-mediated approach for transfection of cells, tissues, and tumors.

SPIONs are attractive materials that are widely utilized in medicine for drug delivery, diagnostic imaging, and therapeutic applications. Akbarzadeh et al. (2012) reported preparation and in vitro analysis of doxorubicin-loaded Fe_3O_4 MNPs altered with biocompatible copolymers. Elbialy et al. (2015) described doxorubicin-loaded magnetic gold nanoparticles (MGNPs) for in vivo targeted drug delivery. Their work was focused on coming up with biocompatible MNPs for use as a nanocarrier in a magnetically targeted drug delivery regimen. MGNPs were prepared, functionalized with thiol-terminated PEG, and then loaded with the anticancer drug doxorubicin. Magnetically targeted drug delivery technology not only minimizes random distribution of the chemotherapeutic agents but also reduces their side effects on healthy tissues, which are the two primary drawbacks of typical cancer therapies.

4.8 Catalysts/Photocatalysts

Nanobiocatalysts are a combination of nanotechnology and biotechnology, and represent an exciting and promising therapeutic domain. Xin et al. (2010) reported protease immobilization on gamma-Fe_2O_3/Fe_3O_4 MNPs for synthesis of oligopeptides in organic solvents. The possibility of using magnetic IONs as enzyme immobilization carriers has drawn attention because of their distinctive properties such as

their controllable particle size, large surface area, modifiable surface, and ease of recovery. These authors studied γ-Fe_2O_3/Fe_3O_4 MNPs with immobilized proteases that were successfully prepared by three totally different immobilization methods: (1) with direct binding, (2) with thiophene as a linker, and (3) with triazole as a linker. The oligopeptide syntheses catalyzed by these MNPs with immobilized proteases were systematically studied, and it was found that the γ-Fe_2O_3 MNPs were better for use as an immobilization matrix than the Fe_3O_4 MNPs because of their smaller particle size and larger surface area.

Wu et al. (2008) described iron compound nanoparticle disposition to oxidation with exposure to air and aggregation in an aqueous solution. Zhou et al. (2011) reported a guided synthesis technique in which a biotemplate was used as an internal or external structure for generation of a nanostructure. Biotemplates, or soft templates, have the advantages of being inexpensive, renewable, eco-friendly, and easily removable. When a biotemplate is used, the biomolecules typically aid nanoparticle synthesis. Mazumder et al. (2016) described use of a reusable magnetic nanobiocatalyst for easy synthesis of silver and gold nanoparticles by reduction of nitrate and auric chloride, employing a nanobiocatalyst. The nanobiocatalyst was prepared by covalent coupling of alpha amylase on (3-aminopropyl)triethoxysilane (APTES)–modified magnetic IONs.

4.9 Future Perspectives

There is an urgent need to further explore plant resources, which are commonly utilized in this field of research, to optimize experimental conditions for preparation of plant extracts—namely, the plant mass–to–solvent ratio, extraction temperature, incubation time, pH, and mixing ratio of the plant extract and salt precursor, i.e., the optimal metal salt solution. The monodispersity and polydispersity, along with the surface area of the biosynthesized nanoparticles, must be optimized. Finally, there is an urgent need to promote as-biosynthesized nanoparticle application in a variety of domains—specifically, health care, environmental science, and agriculture.

4.10 Conclusion

This chapter has highlighted the potentialities and development of iron and iron oxide nanoparticle synthesis mediated by plants in the form of aqueous extracts, which are eco-friendly and economically feasible. Physical and chemical methods for synthesis of these nanoparticles are becoming more common. As-synthesized nanoparticles have been successfully utilized in the fields of medicine and environmental remediation. Iron and iron oxide magnetic nanoparticles are synthesized using plant extracts and microbes, and are coated with water-soluble polymers for high solubility, which prevent aggregation and allow them to easily diffuse through

semipermeable membranes in a living system. Their shapes and sizes can be controlled through control of the temperature, pH, and salt precursor concentration. Their cytotoxicity varies with the shape, size, and paramagnetic/diamagnetic nature of the particles. Superparamagnetic iron oxide nanoparticles have immense potential, due to their magnetic properties, for use in instruments and medical devices, and as drug carriers for the treatment of many diseases. Iron oxide nanoparticles can also be used for removal of dyes in the textile industry, for treatment of contamination in wastewater, and for purification of groundwater.

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