CHAPTER

27

Nano-biomaterials for therapeutic and diagnostic applications

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1. Introduction

Nanotechnology is an extensively developing field of interdisciplinary science that deals with materials in the size range of 1−100 nm[1] called nanomaterials (NMs). It includes nanoparticles (NP), quantum dots (QDs), carbon nanotubes (CNTs), graphene, and their composites. [2−4] Synthesis of NMs with different morphology, structure, size, and their application for the welfare of humanity as a whole is the prime objective of the nanoscience and technology. In the past decade, researchers have paid more attention to nanoparticles owing to their unique attributes such as size, shape, and large surface to volume ratio among others.[5,6] With these unique features, nanomaterials have shown better properties including chemical stability, thermal conductivity, catalytic reactivity, nonlinear optical performance compared to their bulk materials.[7,8]

Besides, NMs could be synthesized with adjustable characteristic properties according to applications and needs.[9] NMs were found to be relevant for a variety of applications in various fields of science and technology but not limited to optical, biomedical, chemical, and energy sciences.[3,6,10−14] Among the various applications of NMs, their utilization in the biomedical field is well established and much attention has been paid in all aspects of their biological applications.[15] NMs can be classified as carbon-based, metallic, metal oxides,

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ceramics, semiconductors, polymeric, and lipid-based NMs.[16,17]Among this classification, metal and metal oxide nanoparticles (MO NPs) have been shown to have potential applications in engineering, agriculture, sensors, and medicine.[18,19]

In particular, metal and metal oxide NPs play a vital role in biomedical applications including antimicrobial therapy, cancer therapy, and diagnostics of several diseases, as well as biochemical sensors, bio-assay, tumor-imaging, drug delivery, and pharmaceutical treatment procedures.[20,21] Hence, various novel metal NMs such as gold, silver, zinc, copper, iron, and their oxide NPs with different shapes and sizes have been synthesized for potential application in therapeutic and diagnosis.[2,6,20,22] Here, we discuss the biological syntheses of some metal and metal oxide nanoparticles as well as polymeric and liposomal NMs and their essential insights and limitations in diagnostic and therapeutic potential for antimicrobial, targeted drug delivery, and immune therapy.

2. Biologically synthesized metal and metal oxide nanoparticles

MO NPs are synthesized by combining oxides of metals from groups 3−12 of the periodic table.[23,24] Generally, MO NPsare prepared via physical methods such as spray pyrolysis,[25,26] ultra-sonication[27] or chemical vaporization.[28,29] Similarly, chemical methods such as sol-gel,[30] hydrothermal,[31] microwave assisted,[32] solvothermal,[33] oxidation-reduction, and chemical precipitation[17,34,35] can also be used to synthesis MO NPs.[36] NPs synthesized via chemical methods are relatively toxic and were found to have, consequently, limited biomedical applications.[19,37] Besides, the solvents and other chemicals used for synthesis are hazardous to the environment that profoundly affects the ecosystem.[19,38] In addition, the yield of chemical and physical methods is low, inhibits particle growth at some point, and generates unstable NPs.[39,40] Interestingly, green syntheses of metal and MO NPs has been recommended as alternative routes to chemical syntheses and put into practice.[39]

Green synthesis refers to the eco-friendly synthesis of MO NPs using plants, microorganisms, and or by their constituents such as lipids, enzymes, carbohydrates, and proteins.[39,41] In some cases, nontoxic, renewable materials, and biodegradable waste products have also been used to synthesis MO NPs.[42] The selection of the primary materials for green synthesis is crucial for adequate stabilization, where natural compounds are desired to act as capping agents to passivate the surface of MO NPs.[6,37,41] Biologically assisted synthesis routes were found to improve the biocompatibility of the synthesized MO NPs.[3,43] Moreover, natural compounds including proteins can serve as reducing, stabilizing, and capping agents thus enhancing the physical and chemical properties and biocompatibility of MO NPs enables for biomedical applications.[44,45] MO NPs are synthesized in two steps referred to as nucleation and growth. For the synthesis of NPs, their respective salts (e.g., Ag NPs—$AgNO_3$, Au NPs—$HAuCl_4$) are added individually to the plant extract or biomass of microbes such as bacteria, fungi, algae, plants (Fig. 27.1).[37,41,46–48]

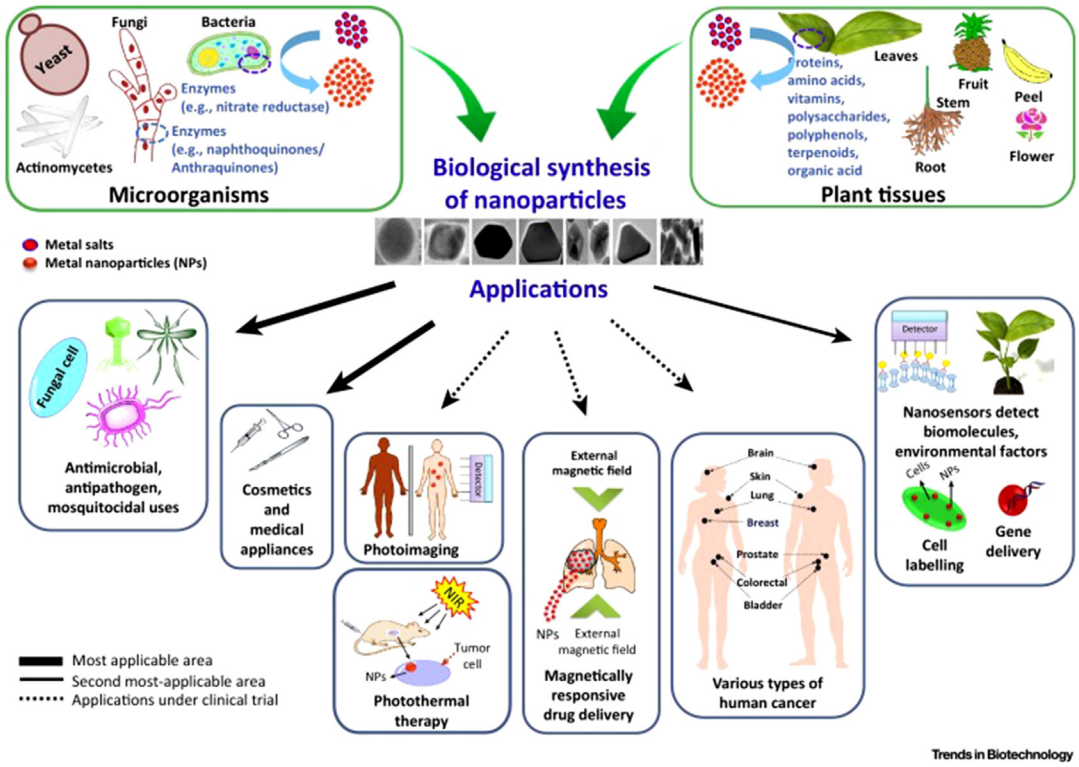

FIGURE 27.1 Metal nanoparticle (NP) biological syntheses and their applications in biomedical and environmental fields. Ag NPs have a wide spectrum of antimicrobial activities and are mostly used as biomedicine, whereas Zn and Ti NPs as cosmetics. Similarly, Ag, Zn, and other metal NPs possess antimicrobial property and are utilized in food packaging, wound dressings, catheters for drug delivery, and other products. In parallel, biological NPs are used as biosensors to detect various biomolecules in environment and agriculture fields. NPs are also used in targeted drug delivery, gene transport, and labelling plant and animals cells for diagnosis. Studies on the development of various NPs for photothermal therapy, magnetically active drug delivery, and photoimaging are ongoing.

2.1 Microbial biosynthesis

Microbial synthesis of metal NPs may be intracellular or extracellular. In the case of extracellular synthesis, the selected metal salts are reduced under the enzymatic action of extracellular enzymes produced by the microbes. In the case of intracellular synthesis, the metallic ions are transported inside the cell, engulfed and reduced to NP and finally excreted out or stored inside the cells.[20,48,49] The properties of the resulting NPs depend highly on the microbial species used during their synthesis.

2.1.1 Bacteria and actinomycetes

Due to their fast growth rate, simple handling and genetically modifiable feature for the bio-mineralization of metals through genetic engineering, bacteria are highly preferable over other methods for the synthesis of metal NPs.[49,50] Bacteria can cope with stress conditions by developing intracellular sequestration of metals, efflux pumps, change in metal ion concentration, and extracellular precipitation.[51] In 1980, Beveridge and Murray reported

the first extracellular bacterial synthesis of NPs by *Bacillus subtilis* that deposited gold NPs on their cell wall. Since then, several studies have reported the ability of bacteria to synthesize NPs as briefly discussed by.[49] Srivastava and Constanti[52] showed intracellular synthesis of Pd, Ag, Rh, Ni, Fe, Co, Pt, and Li NPs by *Pseudomonas aeruginosa*, without addition of any external substance for the formation of NPs.Bacterial strains including *Escherichia coli, B. subtilis, Bacillus megaterium, P. aeruginosa, Klebsiella pneumoniae, Bacillus cereus, Alteromonas, and Ochrobactrum* have been widely used and reported for the synthesis of NPs.[49,51,53] Active biofilms of *Shewanella loihica* PV-4 were found to be able to synthesize ultrasmall (from two up to7 nm) palladium and platinum NPs.[54] *Bacillus brevis* was found to synthesis spherical silver NPs within the diameter size range of 41−62 nm.[55] Recently, marine bacteria were also reported for the synthesis of metal NPs such as silver and gold using *Stenotrophomonas*[56] and copper NPs using *Kocuriaflava*.[57]

Actinomycetes are the repository of novel secondary metabolites and extracellular enzymes.[58] Actinomycetes were also evaluated to obtain NPs by extracellular or intracellular synthesis. Successful synthesis of AgNPs was reported by Otari et al.[59] using *Rhodococcus NCIM*, which paved the way for the synthesis of NPs using actinomycetes. Since then, several groups of researchers have been focusing on the use of acinomycetes for NPs synthesis. AgNPs were synthesized by *Streptomyces* sp. LK-3,[60] *Streptacidiphilus durhamensis*,[61] whereas *Streptomyces griseoruber* and *Streptomyces capillispiralis* Ca-1 were used, respectively, for the synthesis of copper and gold NPs.[62,63] Rajivgandhi et al.[64] reported the synthesis of zinc oxide nanosheets using *Nocardiopsis* sp. GRG1.

2.1.2 Fungi and yeast

Recently, fungal- and yeast-mediated synthesis of metal NPs have been reported as promising approaches for synthesizing NPs since they tolerate, accumulate metals, and their mass cultivation is possible at low cost. Similar to bacterial biosynthesis of metal NPs, fungal mediated synthesis can be either intracellular or extracellular.[65] In addition, size and shape of NPs depend on whether biomass or cell free extract is used for the synthesis.[66] Several reports are available for the synthesis of AgNPs using fungal strains such as *Fusarium oxysporum, Schizophyllum radiatum, Penicillium diversum,* and *Trichoderma harzianum*.[67−70] Similarly, yeast strains such as *Yarrowia lipolytica* NCYC789, *Candida utilis* NCIM 3469, *Saccharomyces cerevisiae*, were also used for AgNPs synthesis.[71−73] Next to AgNPs, AuNPs were prominently synthesized using fungal (e.g., *Rhizopusoryzae, Aspergillus niger, Fusarium oxysporum*)[74−76] and yeast strains (*Candida utilis, Yarrowia lipolytica* NCIM3589)[77−79,80] used *Aspergillus flavus* to synthesis TiO_2 NPs. *Aspergillus fumigatus* were used for the extracellular synthesis of ZnO NPs.[81] Detailed information on the synthesis of metal and MONPs and the factors affecting the synthesis using fungal and yeast strains and their applications were described by Boroumand Moghaddam et al.[65,82] Gajendran et al.[83], Chhipa, H.[84] and Parkash et al.[85]

2.2 Protein or enzyme-based biosynthesis

Microbial enzyme-based NPs synthesis has also been investigated. This method delivers NPs with various size and shape, and usage of different enzyme resulted in different NPs and reaction rate. Besides, during microbial-based synthesis, NPs are bound with the microbial biomass, which requires laborious separation and high cost purification steps.[86,87] The positively charged metal ions (e.g., Ag^+) are able to adsorb onto the negatively charged

surface of the protein through electrostatic interaction. Electron transfer between the metal ion and the protein proceeds and induces the formation of metal NPs.[87,88] In the same way, peptides were also used as reducing and capping agent for the synthesis of metal NPs[87,89,90] and in some cases peptides served as template for the crystal growth of metal NPs.[91]

2.3 Algal-based biosynthesis

According to Fawcett et al.,[92] algae could hyperaccumulate heavy metals and modify them into simple forms and represent a potential source of bioactive compounds such as antioxidants and pigments including carotenoids, chlorophylls, and phycobilins. The presence of carbohydrates, proteins, minerals, oil, fats, and polyunsaturated fatty acids[93] makes them a vital source for the synthesis of NPs. These active compounds both act as reducing and stabilizing agents. The synthesis of NPs may be done by using actively growing cells or dead cells as well as residual biomass or cell free extracts.[94,95] *Chlorella vulgaris* has shown good ability to synthesis Ag and AuNPs using growing and dead cells, respectively.[96,97] Several mechanisms of synthesis have been proposed but the exact mechanism is still elusive. Dahoumane et al.[80] proposed NADH-mediated synthesis of NPs, where electrons from NADH can reduce metal ions. The presence of monosaccharides and polysaccharides, that are present in algae, possess functional groups such as aldehyde, ketone, and hydroxyl groups that act as reducing agents.[98,99] Pigments, such as chlorophyll, fucoxanthin, and riboflavin, act as reactive molecules and trap light; electrons from H_2O that are produced during photosynthesis act as electron donor that can reduce metals.[100,101]

Polysaccharides were extracted from the marine algal biomass and used for the synthesis of metal NPs. Several marine algae including *Pterocladia capillacea*, *Jania rubens*, *Ulva faciata*, and *Colpomenia sinuosa* were used for the synthesis of NPs.[102] Extracts of *Sargassum ilicifolium* were used for the synthesis of AgNPs.[103] The synthesis of NPs based on algae was reviewed briefly by Khanna et al.[102] and Bao and Lan.[94] Arsiya et al.,[104] used crude extract of *Chlorella vulgaris* and Sayadi et al.[105] used *Spirulina platensis* to synthesis Pd NPs. MO NPs such as iron oxide, copper oxide and zinc oxide have been extensively synthesized by using macroalgae. Zinc oxide (ZnO) nanoflowers and cadmium sulfide NPs were prepared from cell free extracts of *Chlamydomonas reinhardtii* by Rao and Gautam[106] and Rao, and Pennathur[107] ZnO NPs were synthesized using *S. muticum*.[30,108] Momeni and Nabipour[109] used *S. bovinum* for the synthesis of octahedral palladium NPs having diameter size between 5 and 10 nm.

2.4 Plant-based biosynthesis

As reported by Mittal et al.,[110] plant-based syntheses of NPs are typically carried out at room temperature and can be accomplished within minutes or can last for a few hours. The compounds present in the extract first reduce the metal salt, which leads to the synthesis of NPs. In addition, these compounds adsorbed onto the surface of the NPs and ensured their stability.[111–114] By following color changes of the reaction media, the successful formation of the respective NPs could be confirmed. Theoretical simulations (e.g., density functional theory (DFT) and molecular dynamics (MD) simulations) have predicted the special binding of a particular phytochemical on metal oxide facets and as a result, the morphology of MONPs

was predicted.[4] Due to the numerous phytochemicals present in plant-extracts, it is difficult to find the exact mechanism of formation using phytochemicals.[115,116]

Several preparation methods can be adopted for the synthesis of single, multimetal NPs and MONPs. Leaf extracts of *Polyalthia longifolia, Catharanthus roseus, Azadirachta indica, Aloe vera,* and *Nerium oleander* were used for the synthesis of AgNPs.[112,117–120] Huang et al.[121] reported the synthesis of Ag and AuNPs using leaf extracts of *Cinnamomum camphora*. Elia et al.[122] used extracts of *Salvia officinalis, Lippia citriodora, Pelargonium graveolens,* and *Punica granatum* for the synthesis of AuNPs. Similarly, leaf extracts of *Evolvulus alsinoides*, bark extracts of *Eucommia ulmoides* and root extracts of *Salvadora persica* were used for synthesizing PdNPs as reported by Gurunathan et al.[77], Duan et al.[123] and Khan et al.[124], respectively. Recently, detailed plant mediated synthesis of nanomaterials was published elsewhere.[115,125,126] CuO NPs were synthesized by using gum obtained from *Sterculia* tree.[127] Ellagic acid extracted from Korean rambutan peel was used for the synthesis of chain-like ZnO.[14] Flower extracts of *Cassia auriculate*[128] and *Vitex negundo*[129] were used for the synthesis of ZnO NPs. Several NMs such as iron, iron oxide, copper, copper oxide, gold, silver, zinc, and zinc oxide were synthesized widely for numerous applications discussed briefly elsewhere.[12,16,130–135] Sometimes, the synthesized NPs are impure, and purification is necessary by either filtration or dialysis. In a study, metal NPs were converted to MONPs after purification by decomposing the NPs (prepared from the sources as described in Sections 2.1–2.4) at relatively high temperature.[136]

Biosynthesis of NPs depends on the solvent used for extraction, reaction temperature, pressure, mixing ratio of the reactants, and pH of the reaction medium. The presence of several chemical moieties in the molecular structure of phytochemicals such as ketones, aldehydes, flavones, amides, terpenoids, carboxylic acids, phenols, and ascorbic acids makes plants excellent choices to synthesis NPs.[137] With respect to microbial synthesis, the selected microbes have to be maintained in the culture media, which is costly and more laborious compared to plant-based synthesis. Also, it is possible to synthesis NPs of small sizes (between 1 and 100 nm)[138] by using plants and sometimes NPs having larger sizes (100–500 nm) were also obtained.[120,139,140] In addition, chemical substances derived from plants are easily available, which promotes rapid synthesis. Finally, the use of plant extracts results in more stable NPs and is suitable for environmentally friendly large-scale synthesis.[141]

3. Polymeric and liposomal nanocarriers

Most of the drugs showing in vitro potency are poorly soluble or insoluble in water, which restricts their usage in clinical applications.[142] These drugs can be conjugated onto surfaces or encapsulated inside the carrier's system to improve their solubility, bioavailability, and biodistribution.[143] The development of nanotechnology offers a wide range of applications in medicine not limited to several diseases including cancer. In this context, NPs have been used as carriers for therapeutic substances such as small drugs, genes, protein-peptides, and imaging contrast agent in diagnosis.[144] Controlled release of these substances is achieved by adequate formulation of the matrix or external stimuli such as pH and/or temperature.[145]

Nano-carriers ensure high bioavailability of the drug by evading reticulo endothelial system. Their small size guarantees high therapeutic efficacy by means of site targeted

delivery.[124,146,147] Properties including circulating durability and stability, targeting capacity, response to stimuli, and diagnostic ability can be improved by surface modification or conjugation with antibodies.[148] For instance, the bioavailability and site specificity of NPs improved while NPs maintained their ability to deliver specific antibody aptamer with improved cancer activity.[147] Nanocarriers are broadly classified as polymer-based or lipid-based systems according to the material used for their preparation. Generally, polymeric nanoparticles, polymeric micelles, dendrimers (polymers), liposomes, solid lipid nanoparticles (lipids), and metal (gold, silver) NPs have shown ability for use as nanocarriers.[147]

3.1 Polymeric nanocarriers

Polymer-based NPs can be made of biodegradable polymers and have been widely evaluated as carriers of drugs, proteins, and DNA to target cells and tissues. These are highly preferable owing to their structural and long-term storage stability, long half-life in blood stream, and high controllable release capability.[149] The use of polymeric nanoparticles (PNPs) as drug carriers has been studied since 1980s. Since then, several PNPs have been developed and mostly used for delivering low molecular weight drugs, proteins, plasmid, and antisense DNA as well as short interfering RNA.[150,151] The preparation of PNPs and their application has been reviewed in detail by Sawdon et al.[152], Kreuter[153] and Amoabediny et al.[154]

PNPs can be prepared using biodegradable, amphiphilic, biocompatible copolymers approved by the Food and Drug Administration. The polymers may be natural (e.g., chitosan, gelatin, sodium alginate and albumin[155] or synthetic (e.g., polylactides (PLA), polyglycolides poly(vinyl alcohol), poly(acrylic acid), polyacrylamide, and polyethylene glycol (PEG)).[155–157] For improving their stability and ability to control the release of drugs, PNPs can be mixed with ligands and antigens.[157] For instance, PEG can be conjugated with polymers for enhancing its immune-compatibility, bioavailability.[158] PNPs can be synthesized using the preformed polymer or synthesized directly during the process of polymerization. Direct polymerization is achieved by microemulsion, mini-emulsion, surfactant free emulsion, and interfacial polymerization. PNPs can be prepared with preformed polymer and dispersed with drugs to avoid toxic, unreactive residues, and unreacted monomers during the polymerization.[159] Solvent evaporation, nanoprecipitation, emulsification/solvent diffusion (ESD), high-pressure homogenization, salting out, dialysis, and spray drying are some of the methods used for the synthesis of PNPs from preformed polymers. Detailed preparation of PNPs and their functionalities can be found elsewhere.[147,156,160,161]

3.2 Liposomal nanocarriers

Liposomes are biocompatible vesicles, hydrophobic and hydrophilic in nature, usually spherical ($\geq$30 nm to micrometers) in shape and typically prepared from cholesterol and natural phospholipids used carriers of drugs.[162] Lipid-based colloidal carriers are nontoxic and used as an alternative to toxic polymeric systems. They are made of one or more lipid bilayers, in which the polar groups are arranged inside or outside of the adjacent aqueous phase. They can be used to encapsulate both hydrophilic and hydrophobic drugs.[163] Lipid composition, surface charge size, and the method of preparation determine the characteristic

features of liposomes. Moreover, the rigidity and charge of the bilayer depends on the components forming the bilayer. For example, unsaturated phosphatidylcholine from egg or soybean phosphatidylcholine (natural origin) is highly permeable and less stable compared with saturated phospholipids with long acyl chains that are rigid and impermeable in nature.[162,164]

Liposomes are smaller (0.025 μm) to larger (2.5 μm) with one or more bilayers. The size affects the circulation half-life of liposome and the amount of drugs encapsulated inside the liposome affected by the size and number of layers. Liposomes are categorized based on their size and number of bilayers as unilamellar (one bilayer) and multilamellar vesicles (more than one bilayer).[165,166] The preparation of liposomes is typically done in following stages: (1) drying down lipids from organic solvent, (2) dispersing the lipid in aqueous media, (3) purifying the resultant liposome, and (4) analyzing the final product.[165,167] Recently,[165] have extensively reviewed the preparation methods of liposomes. Composite liposomes and their drug delivery were published elsewhere[168] for more detailed information about liposomes and their types. Drugs can be loaded into liposomes either passively or actively. In passive loading, the drug is encapsulated along with liposome formation, whereas in active loading, drugs are loaded after liposome formation. The loading efficiency of hydrophobic drugs depends on the solubility of the drug in the liposome membrane. Water-soluble drugs can be effectively loaded by changing pH.[168,169]

More recently, niosomes made of nonionic or amphiphilic surfactants were developed. These are more stable than liposomes and have shown to possess increased transdermal drug delivery ability and were successful used as targeted drug delivery system. Niosomes can be made with or without cholesterol or other lipids.[170] Both liposomes and niosomes provide similar benefits. Niosomes, however, are cheaper and highly stable compared to liposomes.[170] By combining niosome and liposome, biocompatible liponiosome (<150 nm) was developed having the advantages of both carriers. These were found to possess the ability to deliver high amount of both hydrophilic and/or hydrophobic drugs.[171]

4. Metal and metal oxide nanoparticles for antimicrobial therapy

Antibiotics are widely used to combat microbial infections and are considered as one of the major inventions in pharmaceuticals. Recently, however, multidrug resistance (MDR) among the pathogens is considered as common phenomenon and most pathogens have been developing resistance against almost all the available antibiotics. The prevalence of drug resistance threatens the life of humans and become one of the major health or economic issues of the globe in the 21st century.[172] The unique nature of nanomaterials could be potentially utilized to limit and manage the global crisis of emerging microbial pathogens and could contribute to the development of efficient therapeutic solutions. Hence, researches have been focusing on nanomaterials to treat these MDR pathogens and more particularly metal or MO NPs. Researchers involved in the evaluation of nanoparticle as antibiotic have reported that the engineered NPs could efficiently combat MDR strains.[173,174] These NPs are highly stable, durable, and some of them possess low toxicity to mammalian cell lines.[175] By targeting multiple biological molecules including protein and DNA, metal, and MO NPs can act as antimicrobial

agent against MDR pathogens. According to Baptista et al.,[176] and Naveed et al.,[177] MDR pathogens inactivate antibiotics by enzyme, decrease cell permeability, modify target sites/enzymes, and increase efflux via overexpression of efflux pumps for the development of resistance. NPs have the ability to overcome these mechanisms and eliminate the bacterial infections and also inhibit the evolution of resistance.[178] Furthermore, they can improve the activity of several antibiotics by having synergism. For instance, the functionalization of fluoroquinolone with Au NPs was found to improve their efficiency against MDR *Escherichia coli* infections.[174]

Several mechanisms of action have been proposed including biofilm inhibition, activation of host immune system, ROS generation, lipid peroxidation, cell wall/cell membrane damage, inhibition of enzymes, RNA, protein synthesis and proteolysis.[179–181] Also, antitubercular drugs encapsulated by PLG NPs have completely cleared infectious bacteria from the organs of mice. Moreover, the expressions of spaP, gbpB, gtfB, gtfC, ldh, comD, comE, and luxS of *S. mutans* were remarkably downregulated when treated with Ag/ZnO.[182] Similarly, chitosan and chitosan/ZnO nanocomposites have altered the gene expression of quorum-sensing-dependent-virulence factors by repressing LasI and RhlI gene of multidrug resistant *P. aeruginosa*.[183] The chemical moieties present onto bacterial cell wall such as carboxyl, amide, phosphate, and hydroxyl groups act as anchoring sites where the oxide NPs interact, generating ROS and, as a result, induce bacterial death.[180,184] The antibacterial activity is highly depending on the size of the NPs where the activity increases upon decreasing NPs size due to the increasing specific surface area. The importance of shape in the antimicrobial activity, however, cannot be predicted, although limited reports are available. In addition, the mechanism of action is dependent of surface chemistry of NPs.[185] The combined effect of size, shape, ζ-potential, ligands, and material on the mechanism of action of NPs against bacteria is still elusive.[180,186] Singh et al.[37] have reviewed in detail the antimicrobial activity of biologically synthesized metal NPs (Fig. 27.2).

The biological synthesis of these important NPs derived from different natural and renewable resources is discussed in the previous Sections 2.1–2.4. Silver, gold, zinc, copper, silver oxide (Ag_2O), copper oxide (CuO), iron oxide (Fe_2O_3), magnesium oxide (MgO), titanium oxide (Ti_2O), and ZnO are some of the extensively studied metal and MO NPs for their antimicrobial activity.[37,185] Among these metals and MO NPs, silver or its ionic forms have shown the greatest effect on bacteria killing[187] with multiple modes of actions; hence, it was extensively studied and used to treat MDR pathogens.[188] Silver NPs have been used as nanocarriers as well as for the administration of drugs and antibiotics along with silver, showing enhanced effect against MDR pathogens.[189,190] AgNPs possess antibacterial activity against pathogens such as Methicillin resistant *Staphylococcus aureus (MRSA),* Erythromycin resistant *Streptococcus pyogens,* Ampicillin resistant *Escherichia coli,* Vancomycin resistant *Staphylococcus aureus*.[191]

Ag NPs are highly reactive and show high affinity with sulfur group of proteins, enzymes that collapse bacterial cell structure, increase cell permeability and inactivate enzymes. It also binds with DNA and denatures DNA, thereby interrupting replication that leads to cell death.[192–194] Ag NPs have been used as antibacterial, antiviral, and antimycotic agents[195] and coated onto the blades, needles and also on venal, urinary, and drainage catheters.[54]Ag NPs synthesized using fungal strains such as *Fusarium oxysporum, Macrophomina phaseolina* and bacterial strains such as *Xanthomonas* spp, *Sinomonas mesophila* MPKL 26 showed activity

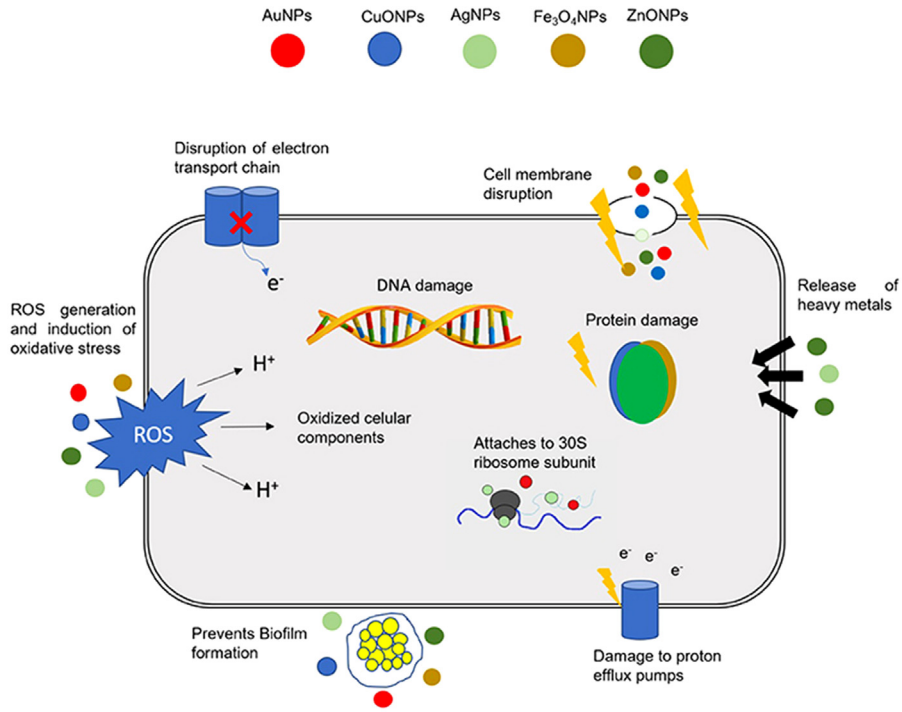

FIGURE 27.2 Plausible mechanism of actions of nanoparticles (NPs) in bacterial cells. The synchronized action of various mechanisms of nanoparticles that exert antibacterial activity may have a significant influence in combatting MDR bacteria.

against MRSA and beta-lactamase producing strains, ampicillin, and chloramphenicol resistant *E. coli, P. aeruginosa,* and *S. aureus*, respectively.[196–199] Cubic, triangular, spherical, and fiber-like shaped AgNPs synthesized by using leaf extract of *Solanum nigrum* and other plant species showed antibacterial activity against six MDR bacterial strains and antibiofilm activity against *P. aeruginosa* and *S. epidermidis*.[200–202] According to Das et al.[39] and Dash et al.[200]; AgNPs synthesized using leaf extract of *Ocimum gratissimum, Cinnamomum tamala* generated intercellular ROS that effectively kills MDR *E. coli* and *S. aureus* cells. Alavi et al.[203] showed that Ag NPs synthesized using *Protoparmeliopsis muralis* was highly effective against planktonic and biofilms of *S. aureus* ATCC 43,300 (MDR), *E. coli* ATCC 25,922 and *P. aeruginosa* ATCC 27,853 than Cu, TiO_2, ZnO, and Fe_3O_4 MO NPs.

Similar to Ag NPs, Au NPs have also been widely used as antibacterial agent against clinical pathogens due to their high biocompatibility. Au NPs can be used alone or incorporated with biomolecules such as collagen, chitosan, or with antibiotics or antibodies.[37,204] For instance, the incorporation of ampicillin was found to increase the antibacterial effect of AuNPs against ampicillin bacteria.[205] Au NPs enters the cell, destabilize ATP synthase as well as cell membrane potential that results in cell death. Furthermore, the multivalence of ligand functionality of AuNPs efficiently makes them interact with cell surface of the bacteria.[206] AuNPs synthesized using the methanolic leaf extract of *Clitoria ternatea* showed strong activity against MDR gram-positive (*S. aureus, S. epidermidis*) and gram-negative bacteria

(*E. coli*, *P. aeruginosa*) and showed QS-based antibiofilm activity.[207] Nontoxic and biocompatible AuNPs prepared from aqueous peel extract of *Musa paradisiaca* showed antibiofilm activity against antibiotic resistant (MARS) gram-positive *Enterococcus faecalis*.[208] Boda et al.[209] utilized Au nanoclusters against planktonic and biofilm forming MDR pathogenic *Staphylococci*. Au NPs possess synergism when loaded along with antibiotics. For instance, lysozyme-capped Au NCs (Lys-Au NCs) with β-lactam antibiotic ampicillin (Lys-Au NCs-Amp) revert the MRSA resistance and also kills the nonresistant bacterial strains.[210] Gandhi and Khan[211] developed bacitracin-templated Au nanoclusters to combat MDR pathogens. Mohamed[212] synthesized ampicillin-loaded AuNPs that showed potential activity against ampicillin-resistant bacterial strains including *MRSA, P. aeruginosa, Enterobacter aerogenes* by reducing the level of beta-lactamase and inhibiting transmembrane pump that catalyzes drug efflux.

Zinc and zinc oxide NPs (ZnO NPs) have been used as antibacterial and antifungal agents. Several studies demonstrated their good biocompatibility and low toxicity.[37,213] The bacterial surface possesses proteins, and the cell walls are composed of polysaccharides and tiechoic acid, which helps bacteria to thrive in host defense and harsh environmental conditions. These are charged molecules and surface modified ZnO NPs specifically elicit damage on the cell wall of the bacteria.[214] ZnONPs showed antibacterial activity against *E. coli, Listeria monocytogenes, Salmonella,* and *S. aureus*.[213,215] ZnO NPs are highly conductive and hence absorbs more UV light, which causes desorption of oxygen from its surfaces that enhances the interaction of ZnO with bacteria. The level of ROS was found to be higher when ZnO NPs were illuminated with UV light and showed efficient antibacterial activity.[216,217] UV light illuminated ZnO NPs were found to show increased oxidative stress against cells by producing superoxide, hydroxyl, and singlet oxygen radicals. Extracellularly synthesized ZnONPs by using the supernatant of *Escherichia hermannii* showed antibacterial activity against urinary tract infective MDR pathogenic strains of *E. coli* and *K. pneumoniae*. The authors showed that the ZnONPs interacted with the cell wall of the bacteria and destabilized it by ROS production, leading to cell death.[218] Similarly, Maruthupandy et al.[203] synthesized ZnO NPs using *Camellia japonica* leaf extract, which showed inhibitory effect against extended spectrum β lactamases (ESBLs) producing clinical strains of *E. coli* and *P. mirabilis* with minimal inhibitory concentration (MIC) percentages of 83% and 81% at 100 μg/mL, respectively. Likewise, ZnO NPs synthesized using root extract of *Raphanussativus* showed higher antimicrobial activity against *Escherichia fergusonii* (MDR) and *Escherichia coli* strains than chemically synthesized ZnO NPs.[154] Most of the virulence genes are down regulated in the presence of ZnO NPs, which confirms the effective treatment of ZnO NPs.[118]

Likewise, iron oxide (FeO) NPs showed activity against human pathogens such as *S. aureus, S. enterica*, *P. mirabilis, E. coli, P. aeruginosa, Pasteurella multocida, P. aeruginosa* and *S. typhi* and plant pathogen *Ralstoniasolanacearum* synthesized using plants *G. jasminoides, L. inermis, Skimmia laureola,* and *M. oleifera*.[219–221] Fe-based NPs were also used as coating materials for medical devices and textiles against bacterial and fungal infections. Furthermore, they possess similar advantages compared to other metal NPs and in addition they can be recovered from the environment using magnets owing to their magnetic properties.[222,223] In the same way, Muthukumar et al.[224] synthesized FeO NPs using *Azadirachta indica* leaf extract and tested their antibacterial and antibiofilm activity against *P. aeruginosa, S. aureus, K. pneumoniae* L. *sphaericus, and B. safensis*. The study showed that these FeO NPs were

more active against gram-positive than gram-negative bacteria due to the presence of thick peptidoglycan layer onto the surface of gram-positive bacteria. FeO NPs were also found to inhibit more efficiently the biofilm formation of gram-negative bacteria than gram-positive bacteria since the NPs could efficiently diffuse when the hydrophilic bacterial surface turned into hydrophobic surface that attracts the NPs.[225] Very recently, FeONPs synthesized using *R. tuberosa* leaf extract were coated onto cotton fabric and were found to be active against *K. pneumoniae*, *E. coli* and *S. aureus* bacterial strains. They suggested that the synthesized FeO NPs could be used as coating materials onto the readymade fabrics, uniforms, and laboratory coats used in hospitals.[226] The positively charged FeO NPs tend to attach onto the surface of the negatively charged cell wall of the bacteria, resulting in increased attachment of NPs and destabilization of cell wall inducing bacterial death.[227]

Copper-based NPs are semiconductors that have a narrow band gap; Cu and copper oxide (CuO) NPs have been shown to have antimicrobial activity toward wide ranges of bacterial and fungal pathogens via ROS mediated mechanism.[228] Rajivgandhi et al.[229] successfully used CuO NPs synthesized using leaf extract of *Camilla japonica* against ESBL producing urinary tract infecting pathogens such as *P. aeruginosa* and *K. pneumoniae*. CuO NPs act on the bacterial cells and alters the intracellular signaling pathways that controls the oxidative stress, leading to cell lysis.[230] Ashajyothi et al.[231] synthesized Cu and ZnONPs extracellularly using *Enterococcus faecalis* and tested antibiotic activity against clinical pathogens *E. coli, K. Pneumonia, methicillin-resistant S. aureus (MRSA)*and non-clinical strains*P. aeruginosa MTCC 741, S. flexneri MTCC 1457,* and *E. faecalis NCIM 5025*. They found that both NPs were active against both gram-positive and gram-negative pathogens and also inhibited the biofilm formation of all pathogens except *P. aeruginosa.* They concluded that Cu NPs are more effective than ZnO NPs. Studies from several researchers suggested that Cu NPs were highly active against MDR*P. aeruginosa* and *MRSA* pathogenic strains, similarly to the activity of AgNPs.[232,233] According to Meghana et al.[234]; CuO NPs always generate ROS that specifically affects the chromosomal DNA rather than other molecules that highlighted the particle specific activity of CuO.

Titanium dioxide (TiO_2) NPs are chemically stable, nontoxic, and possess wide applications. They are more particularly used in the formulation of cosmetics owing to their UV radiation absorption ability.[235] TiO_2 NPshave shown to have antibacterial activity against most bacteria.[63] Similar to previously discussed metals and MO NPs,TiO_2NPs also generate ROS and kill bacteria by adhering onto the surface of the bacterial cell wall and produce ROS that act on phospholipids present on the cell wall of the bacteria by lipid peroxidation.[236] This destabilizes cell membrane and causes damage to the cellular components, particularly on DNA and is followed by cell death.[237–239] Very few reports are available on the preparation of TiO_2 NPs using biological materials for antimicrobial applications. TiO_2 NPs prepared from *Psidium guajava, Prunus yedoensis* showed bactericidal property against *E. coli and S. aureus*.[240,241] TiO_2 NPs synthesized using *Aloe barbadensis mill* were active against *P. aeruginosa* PAO1.[242] Likewise, Subhapriya et al.[243] synthesized TiO_2 NPs using *T. foenum-graecum* leaf and showed effective activity against *Y. enterocolitica, P. vulgaris, E. faecalis, P. aeruginosa, S. faecalis, S. aureus, B. subtilis, E. coli and fungus C. albicans*. TiO_2 NPs also synthesized using *Streptomyces* sp. HC1 showed antimicrobial activity toward several pathogens such as *E. coli, S. aureus, C. albicans, and A. niger* and antibiofilm activity against *P. aeruginosa*.[244]

Other than these metals, several metals NPs such as aluminum, palladium (Pd), selenium (Se), and cerium were also evaluated as antimicrobial agents. PdNPs[245] and cerium NPs[246] synthesized using peel extract of *M. oleifera* showed antibacterial activity against *E. coli* and *S. aureus*. Pd NPs synthesized using *F. decipiens* leaf extract and *C. guianensis* fruit extract were effective against several human pathogens and the effect was found to be oxidative stress mediated.[247,248] Se NPs synthesized using bacterial sources such as *B. licheniformis* JS2,[249] *S. maltophilia, B. mycoide*,[250] *S. aureus, P. aeruginosa*, and *E. coli*[251] showed potential activity against bacteria and fungus, and on their biofilm formation. Even if antibacterial effects have been proven in preclinical studies, evaluation of therapeutic efficacy in clinical trials and the safety of NP systems is essential.[186] The economic impact of clinical translation of NPs must be addressed with regard to their therapeutic efficacy.[186,252]

5. Targeted drug delivery and disease diagnosis

Recent researchers have been mainly focusing on developing compounds from natural resources to find novel drugs for treating major diseases such as cancer, diabetes, heart diseases, inflammatory, and microbial diseases due to their least toxicity, side effects, cost, and higher efficiency.[253] These active materials often delivered with larger delivery systems, which have several limitations such as low biocompatible, toxic, poorly soluble, unstable, poor bioavailable, targeted delivery issue, and tone effect, and side effects of medicines. To overcome these pitfalls, NPs have been developed as delivery systems and offer time-controlled or targeted-delivery of drugs.[137] NPs increase the bioavailability and stability of the drug as well as the delivery drugs at specific sites and consequently increases the efficiency of delivery systems.[129] Furthermore, NPs are smaller in size and it could deliver various genes, vaccines, proteins, hydrophobic and hydrophilic drugs to the different part of the body including brain, arterial walls, lymphatic system, liver, spleen, lungs.[254,255] The rate of degradation and drug release could be easily adjusted by using polymers.[256] Polymeric and liposomal NPs-based delivery systems are briefly discussed in Section 3.

Liposomes were the first developed and approved nano-carrier based on lipids that can deliver inorganic NPs such as gold and iron NPs, which increases their used for drug delivery, imaging and other treatments.[129,205,257] Also, the addition of NPs could increase the bioavailability and control the release of drugs. For site specific drug delivery applications, metal as well as organic, inorganic, and polymeric nanomaterials were used particularly for delivering poorly soluble and least absorption drugs.[258,259] These systems were designed to deliver the drugs at specific place or for controlled release of the drug at specific sites and to overcome the opsonization/sequestration of phagocytosis.[260] Nanostructures convey drugs either by self-delivery or passive delivery. In self-delivery, the drugs are directly linked with the carrier to facilitate the delivery whereas in passive delivery the drugs are loaded hydrophobically in the inner cavity of the nanostructure. These were found to encounter the specific site and release the planned amount of drug since lower amount of drug was encapsulated in hydrophobic environment.[162] It is possible to deliver drugs using NPs and the loading of drugs into the NPs are classified as active or passive targeting. In active targeting, the drugs are loaded with the delivery system that carry site-specific antibodies or

peptides, which could bind onto the receptors of the particular site. The drugs delivery system circulates in the blood stream and delivers the drug in a particular site due to changes in pH, temperature, molecular site or/and shape.[41,261] Mostly, these drug delivery systems are used for treating cancer.

Drug, gene and protein delivery of Au NPs have been reviewed by researchers.[41,262,263] Similar to liposomes, Au NPs can deliver several recombinant proteins, DNA, vaccines, and antibiotics. AuNPs have been used for treatment of cancer therapy and successfully crossed the blood brain barrier when loaded with human serum albumin. In addition, this was achieved due to the lower surface charge, albumin layer, and the capacity to absorb huge amount of creatine.[264] Antibiotics are typically loaded onto AuNPs via ionic or covalent bond, and the ampicillin functionalized AuNPs were found to be able to revert the drug resistance of the MDR pathogens.[265] Also, functionalization of Au NPs with ampicillin, streptomycin, and kanamycin demonstrated efficient antibacterial activity.[244,266] AuNPs provide uniform size, similar surface properties, and increased biocompatibility when encapsulated in alginic acid-poly[2-(diethylamino)ethyl methacrylate] monodisperse hybrid nanospheres. Human colorectal LoVo cancer cells uptake more these negatively charged nanospheres and hence were used as optical sensor for tumor imaging along with inhibition.[267]

Conjugating AuNPs with 2,5-diphenyltetrazole and methacrylic acid, shifted AuNPs plasmon resonance to near infrared (NIR), which increases the photothermal efficiency of breast cancer treatment.[268] Recently, [58] showed the delivery of small molecules for targeting lymphocytes and Dhanya et al.[269] observed better transfection efficiency when arginine conjugated AuNPs were caped with starch and polyethyleneimine. Munsell et al.[270] developed efficient histone-inspired scaffolds using AuNPs adorned with histone motifs for delivering genes and chromatin analysis. In another study, noncovalently conjugated AuNPs-siRNA covered with a lipid layer efficiently delivered siRNA into cell, followed by specific gene silencing.[271] In MCF-7 cells, lipid-coated AuNPs showed nearly 85% of gene transfection efficiency facilitated by folic acid (FA) based ligands.[272] Iron oxide NPs have been extensively used as cancer therapeutic agent with high degree of specificity. It is possible to control the particle through external magnetic field that improves the release of dexamethasone acetate in vivo.[43] A study by Jain et al.[273] clearly demonstrated the biosafety of these magnetic NPs while testing them intravenously. These were found mostly in the liver and spleen rather than in other organs. Similarly, long-term exposure of magnetic NPs did not exert oxidative stress in the cell or change liver enzyme levels suggesting good biocompatibility. Paclitaxel-loaded chitosan oligosaccharide (PTX-COS) stabilized AuNPs could deliver and release drug by pH dependent manner. The synthesized PTX-COS AuNPs showed strong cytotoxicity against MDA-MB-231 cells by means apoptosis. The increased ROS generation and altered mitochondrial membrane potential (MMP) level caused cell death (Fig. 27.3).[274]

Nanoscaled diagnostics offer new alternatives for portable and sensitive health monitoring that can guide the use of nanoscale immunotherapies. As metal-based nanoparticles (gold, silver and silica) and polymer-based nanoparticles (chitosan, dextran, polyethylene glycol (PEG) and polylactic-co-glycolic acid (PLGA)) possess photo-based imaging ability. These can act as nanocarriers to deliver various fluorescent dyes or photosensitizers for photoimaging and therapeutic applications including magnetic resonance imaging (MRI) and optical imaging to photothermal therapy (PTT) and chemotherapy.[2] In early 90s′, iron oxide

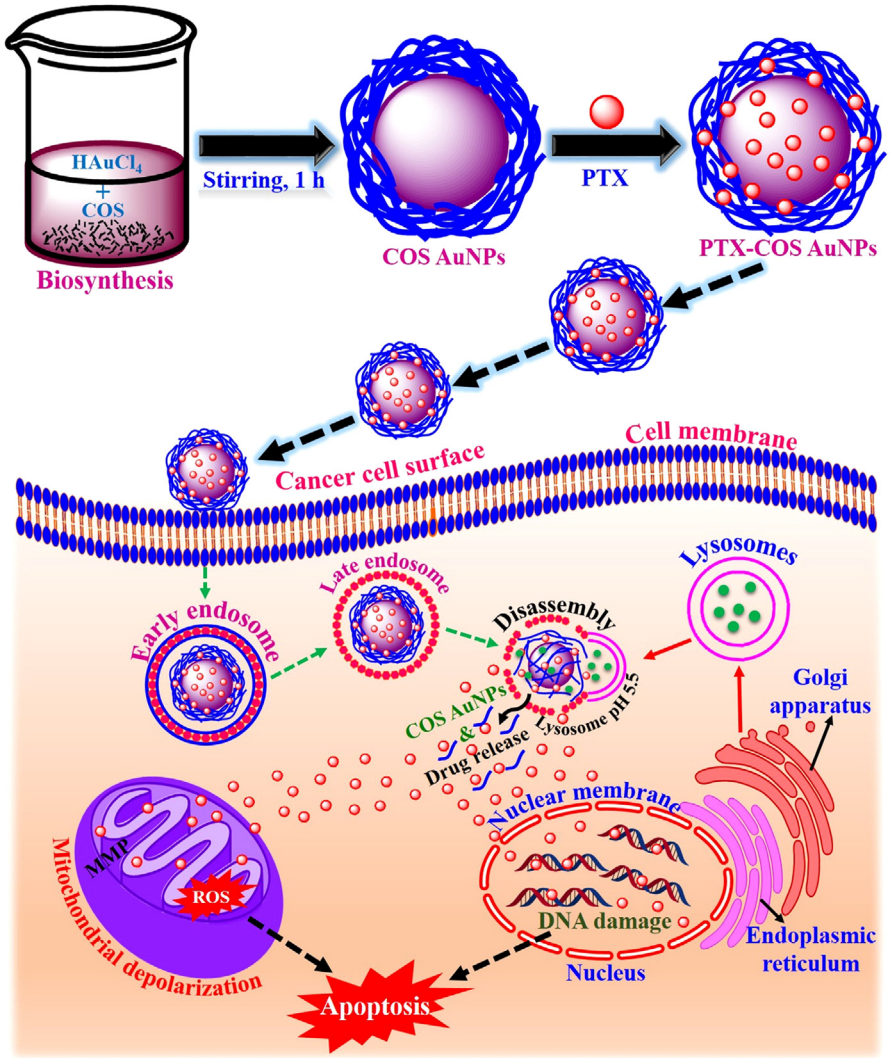

FIGURE 27.3 A general strategy for the biosynthesis of gold nanoparticles (Au NPs) using chitosan oligosaccharide, followed by loading of paclitaxel (PTX) on stabilized Au NPs made of chitosan oligosaccharide (COS Au NPs), and a potential mechanism for cellular uptake and mode of action of paclitaxel-loaded COS Au NPs in MDA-MB-231 cancer cells.

nanoparticles with magnetic properties have been used as vascular contrast agent for MRI.[275] AuNPs have been functionalized for the detection of biological molecules (DNA and proteins), heavy metals, and glucose as well as microbes.[276–278] In 2008, Huang et al. developed optically responsive gold nanorod (GNR)-elastin-like polypeptide (ELP) nanoassemblies that showed phase transition and aggregation of NPs upon NIR irradiation, which could be used for drug sensor and drug delivery.

PEGylated AuNPs showed Raman scattering efficiency increased by 14−15 orders of magnitude, which could be applied for detecting cancer cells in animals.[279] Similarly, PEGylated AuNPs demonstrated ability for imaging tumor and blood cells since they can be easily distributed and stabilized in aqueous solutions.[280] It was shown that size, shape, and structure of Au NPs affect their scattering property. Very recently, biocompatible deferrioxamine conjugated to PEGylated Mn(II) complex gold nanoparticles could be used as dual imaging system in MRI and CT scan and also effective against 4T1 breast tumor-bearing BALB/c mice.[281] Similarly, AuNPs in the size range of 30−100 nm were found to scatter light strongly, which can be detected using dark-field microscopy imaging.[282] Huang and El-Sayed[282] prepared spherical AuNPs (40 nm) conjugated with epidemic growth factor (EFGR). After 4 min of exposure to laser light, head and neck cancers could be detected. Tabrizi et al.[283,284] developed inexpensive and highly selective electrochemical aptasensors based on MWCNTS-PdNano/Ptca and Au@AgNPs for counting leukemic lymphoblast and adenocarcinoma gastric cancer cells. AuNPs modified with PEG and polyethylmethacrylate (PEMA) showed efficient tumor detection when used along with antitumor drug daunorubicin.[285] Recently, a brief review on application of gold NPs in cancer therapy and diagnosis is published elsewhere.[286]

6. Nano-vaccination and immunotherapy

Vaccination is an important achievement of medical science that helps human beings to survive against several epidemics and pandemics. Vaccines induce immune response and provide lifelong protection and it may contain inactivated, killed, or attenuated microbes. The main objectives of effective vaccines design are successful presentation of antigens to antigen presenting cells (APC), the ability of APCs to process antigens[287,288] and present them to T-cells along with MHC and other costimulatory cells.[289] APC internalize and process antigens and hence matures and migrates to lymph nodes and present the antigen to T-Cells. Development of new vaccines for emerging infectious diseases and improvement of existing vaccines against specific diseases is the major concern of pharmaceutical industries.[290] Vaccines failed, however, to protect some patients and also pose health risk due to reversal of virulence.[291] In addition, vaccines should also induce immune response to cancer, HIV, malaria, and tuberculosis. Nanotechnology has been recently involved into vaccine development to overcome the drawbacks of conventional vaccination progress by developing nanocarrier-based delivery systems to increase cellular and humoral immune responses and slow release of targeted delivery. Scientists believed that nanovaccines could overcome pathogen-mediated evasion of the immune response and induce specific cytotoxic T-lymphocyte (CTL; activated CD^{8+} T cell).[292,293] Nanoparticles used as adjuvants can facilitate the uptake of vaccine antigen by APCs and achieve efficient antigen recognition and presentation to target specific receptors onto the cell surface to stimulate selective and specific immune responses.[294]

In the last 2 decades, several particles with different physicochemical characteristics have been evaluated for delivering antigens, such as (co)polymers, liposomes, mesoporous silica, chitosan, and particle size and found to control the immunological fate of their biodistribution, pharmacokinetics, efficacy, and cellular internalization.[295−299] Usually, NP based vaccines target Dendritic Cells (DC) and sometimes targets lymph nodes with APCs

that eliminates premature antigen presentation.[300] Nanovaccines itself elicit themselves immune response however the immune response is not enough to maintain its activity and also tumor- or tissue-infiltrating ability of T cells. Hence, combination of nanovaccines and immune modulators could be used as a therapeutic agent. For example, combination of nano disc vaccine and anti-PD-1, anti-CTLA-4 can destroy cancer cells.[301] Similarly, antigens were combined with several Inorganic NMs such as gold NPs, quantum dots, silica NPs, carbon nanotubes, and iron oxide NPs and subsequently used as vaccines to stimulate immune response against infectious disease.[302–307]

Use of Poly (lactic-co-glycolic acid) (PLGA) as a nanocarrier for imaging, drug targeting and therapy have gained more attention due to their biocompatibility and degradation potential. Cisplatin-loaded poly(L-glutamic acid)-g-methoxy poly(lactic-co-glycolic acid) nanoparticles were developed for treating lung cancer[308] and their recent advancement has been reviewed by Farooq et al.[309] Similarly, spherical PLGA-NPs were used to encapsulate an inactivated Swine influenza virus (SwIV) H1N2 antigens and tested for treating swine flu.[310] Several types of formulations have been recently developed for various diseases, suitable vaccine formulations, toxicity assessment, drug solubility rate, and saturation but storage seems to be a challenge.[164,311] Chitosan and pullulan (natural biopolymer-based nanodelivery systems) have been tested on animals as vaccine and adjuvant delivery systems and the results revealed that vaccination doses of the antigen entrapped in nanoparticles via intranasal induced higher systemic and mucosal antibody responses. Likewise, chitosan NPs loading plasmid DNA encoding nucleocapsid protein of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) for nasal immunization in mice has been studied.[312] Therefore, nanocarrier-based delivery systems could provide a suitable route of administration of vaccine molecules and enhance cellular uptake thereby resulting in the induction of innate and adaptive immune responses against infectious diseases.[313] Development of multifunctional nanovaccines significantly increased stability, sustained release of antigens, lowered immunotoxicity, increased target-specificity, facilitated modification of nanoparticle surfaces and ability to codeliver antigens along with adjuvants that may potentially be used more broadly for the prevention and treatment of infectious disease and cancer.[314] For instance, GNPs contains high-mannoside-type oligosaccharides (P1@HM) and HLA-A*0201-restricted HIV-peptides showed increased DC activity that resulted in high level of HIV-specific CD^{4+} and CD^{8+} T-cell proliferation and cytokine secretion. The results of the study would be promising approach for improving HIV vaccines (Fig. 27.4).[315]

In animal models, gold NPs are effective immunotherapeutic against several contagious diseases including HIV, malaria, listeria, and parasitic diseases.[302,316–319] Additionally, the size-dependent effect of AuNP has been tested against its response on viral proteins (NP-displayed foot-and-mouth disease related peptide).[320] In a study, codelivery of AuNPs with ovalbumin (OVA) was found to stimulate Toll-like receptor 9 (TLR9), in which the immunization with AuNps along with treated DCs showed reduced viral removal than mice immunized with DC and control.[307] AuNPs are considered as Class B Select Agent and were found to protect the immunized animals against Burkholderia mallei when conjugated with LPS and protein carrier.[321]

Cancer cells are surrounded by immunosuppressive microenvironment that restricts the immune system to recognize and kill cancer cells. Hence, treating cancer even in the era of

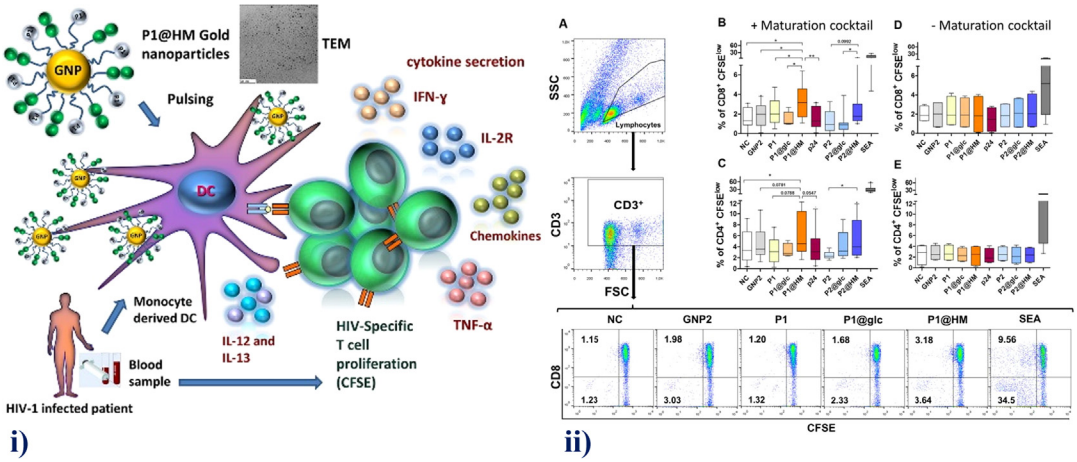

FIGURE 27.4 (i) Representation of the development of GNP formulation conjugated with HLA-restricted HIV peptides and mannosides, and loaded with dendritic cells for the enhancement of HIV-specific T-cell responses. (ii). Response of cell in terms of T-cell proliferation in response to autologous MDDC pulsed with peptide@manno GNPs.

the advanced science is still a challenge. Further, the available methods including chemotherapy radiation have several side effects.[302] Recently, researchers found that the delivery of OVA and cytosine-phosphate-guanine (CpG) motif on polypropylene sulfide NPs delayed tumor growth of thymoma cell line.[322] Iron oxide NPs are superparamagnetic particles, which could be used to target immune signals because it can evade biological barriers and visualized using high-contrast MRI at cellular level.[323,324] Being magnetic and owing to their ability to imaging eliciting immune signal, iron oxide NPs can be used as immunotherapeutic agents against several diseases particularly to cancer. For instance, dimercaptosuccinic acid (DMSA)-coated magnetic NPs were found to possess ability for adsorbing the antitumorigenic cytokine IFN.[323] Similarly, iron oxide–zinc oxide core–shell NPs were used to target DCs for cancer therapy and imaging applications (Fig. 27.5).[325]

7. Conclusions and future perspectives

The biologically synthesized metal and metal oxide NPs possess interesting advantages compared to the chemically synthesized NPs, which include biocompatibility, low cost, and environmental friendliness. As discussed above, metal and metal oxide NPs have potential biomedical applications in treating infections and targeted drug delivery systems. Also, functionalization of these NPs could be used as nanovaccine and improved immunotherapy cancers and diseases. However, knowledge on the bioactive material responsible for the formation of NPs during biosynthesis is still limited since the biological molecules are responsible for both biocompatibility and stability, and more information on this is needed for the biofabrication of desired NPs. Several groups of researchers have been focusing on the largescale production of biosynthesis of smaller sizes with reproducibility and commercialization. Large-scale production biosynthesized NPs are still at its infancy and still need improvement and optimization. Though metal and MO NPs are effective against drug

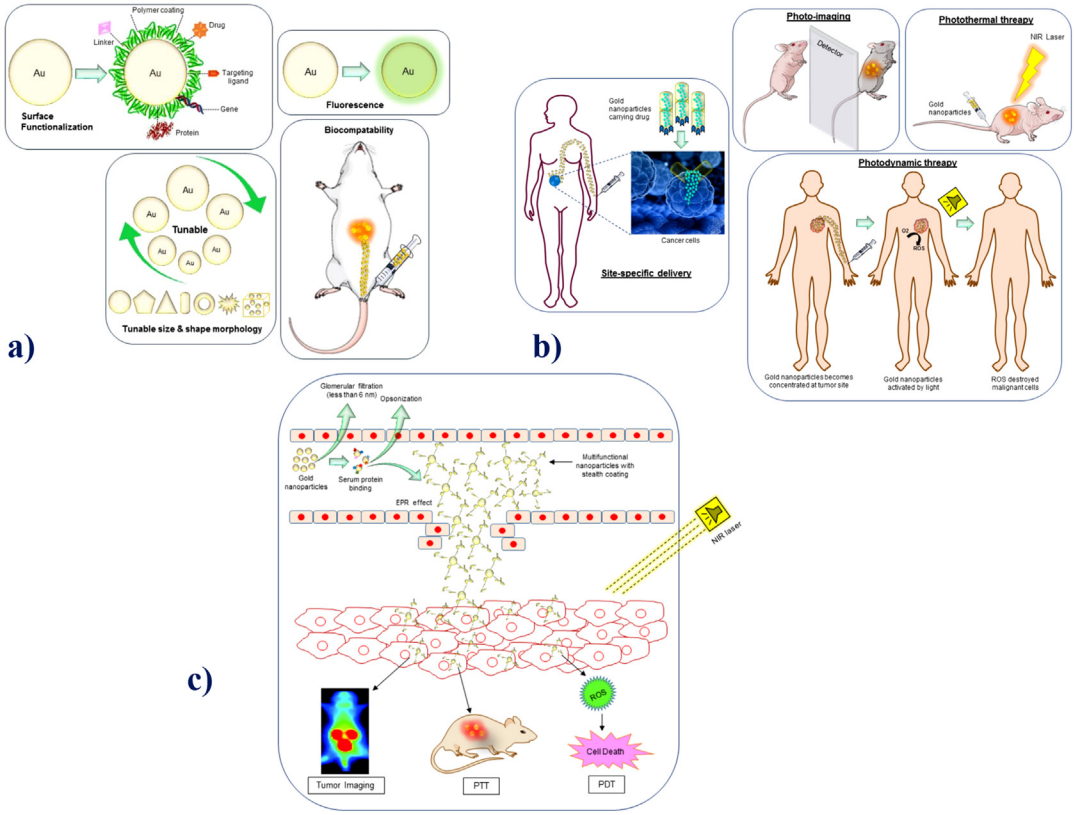

FIGURE 27.5 a) Key features of gold nanoparticles (Au NPs). B) Various methods of detection and treatment of cancer using Au NPs. C) Systemic administration of multifunctional Au NPs for photothermal therapy (PTT), photodynamic therapy (PDT), and cancer bioimaging. NIR = near infra-red, ROS= reactive oxygen species.

resistant pathogens, information on their metabolism, clearance, toxicity, and in-depth knowledge on the pharmacokinetics/pharmacodynamics is very limited. Further, the environmental fate and behavior of the NPs is not yet fully understood.

Functionalization of NPs with ligands can be accomplished by means of surface modifications that enable them to interact with biological molecules and make them as important tool in nanomedicine. These nanomedicines have several advantages not limited to site targeted drug delivery, controlled drug release, stability, improved bioavailability, and biocompatibility compared to conventional medicines. They could be potentially used as vaccines immunotherapeutics and early diagnosis of diseases. Some are already available in the market and in some in clinical trials. However, these are only efficient at preclinical stages. Only very few of them successfully translated to clinics. Other ones are already available in the market, but their clinical translation is a major hurdle. The clinical trial framework for the nanomedicine must be improved to ensure quality and safety of nanomedicine. The encapsulated drugs have higher half lives in the body, but their long-term side effect of the nanomedicine needs

to be deeply studied. Further, detailed toxicological profile of these nanomedicines is essential, and more research should focus on these aspects before clinical trials. Development of nanocarriers is also an important factor for the translation of these medicines to clinics. Collaborative interdisciplinary research all over the world is necessary for clinical use of these NPs as therapeutics and diagnosis.

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