Biofilm Inhibition by Nanoparticles

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Abstract Infectious diseases are of immediate concern due to their high rate of morbidity and mortality. Infectious diseases are life threatening in the current scenario as the causative agents are resistant to almost all the drugs in use. Apart from well-known factors like efflux pumps, receptor modifications, and drug inactivation, formation of biofilms attributes to broad-spectrum resistance toward antimicrobials. This necessitates the search for novel therapeutics that effectively control drug-resistant pathogens. Targeting biofilm formation is one such strategy to combat infectious diseases much more effectively. For over a decade diverse sources of synthetic to semisynthetic agents derived from microbes to plants have been tested for their antibiofilm potential with limited success. The birth of nanotechnology provided new insights into antibiofilm research as these nanoparticles are highly reactive and effective in penetrating the biofilm matrix. This chapter comprehensively summarizes the synthesis, application, weakness, and antibiofilm potential of nanoparticles.

1 Introduction

Infectious diseases are of major concern as they can result in high mortality and morbidity. Bacteria and fungi are the major pathogens that cause infections in humans and development of resistance by these organisms contributes to the severity of infections. Diseases caused by multidrug-resistant (MDR) pathogens are extremely difficult to treat and have a major impact on the economy. Even though numerous mechanisms like activation of efflux pumps, decreased permeability to antagonists, production of enzymes (e.g., beta-lactamase to inactivate antimicrobials), and mutation in target proteins facilitate resistance, biofilm

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formation has been the predominant mechanism of broad-spectrum tolerance. Biofilm are complexes made up of microbes surrounded by a hydrated matrix that is secreted by these indwelling microbes to protect or facilitate their growth in hostile environments. Biofilms are characterized by their extracellular polymeric substances (EPS) which contain polysaccharides, proteins, lipids, and nucleic acids. Apart from conferring resistance to the inhabitants, biofilms also facilitate various other functions like aggregation, retention of water and nutrients, absorption of nutrients, protection against host immune responses, and horizontal gene transfer. Studies have even suggested that the multicellular behavior of biofilm inhabitants is similar to higher multicellular organisms.

In theory, antibiofilm agents are less likely to cause selective pressure for the evolution of resistance because they do not kill pathogens as do antibiotics. Successful antibiofilm agents can either inhibit the formation of biofilms or disrupt mature biofilms. Antibiofilm agents are preferred over antibiotics in some instances as they prevent or disrupt biofilms, facilitating their clearance by the host immune system. Numerous sources from soil to sea and herbs to plants have been screened for antibiofilm activity. Even, some antibiotics have been shown to possess antibiofilm activity at sublethal concentrations. In addition, synthetic agents with antibiofilm properties are of interest because of their feasibility and availability for application.

Various agents such as synthetic chemicals, microbial secondary metabolites, phenolic compounds and other phytochemicals from plants, antibiotics at their sublethal concentrations, nucleases, proteases and other enzymes, peptides, etc., were shown to have the potential to inhibit biofilm formation and/or disrupt mature biofilms. Numerous synthetic chemicals like thiazolidinone derivatives (Pan et al. 2010; Rane et al. 2012), aminoimidazoles (Furlani et al. 2012), diazopyrazole derivatives (Raimondi et al. 2012), bromopyrrole alkaloids (Rane et al. 2013), etc., were shown to have antibiofilm potential against Gram-positive bacterial pathogens like *Staphylococcus aureus*, *Streptococcus epidermidis*, and *Enterococcus faecalis*. Other synthetics like niclosamide (Imperi et al. 2013), esomeprazole (Singh et al. 2012), chlorogenic acid (Karunanidhi et al. 2013), and zinc (Wu et al. 2013) showed promising results against various Gram negative bacteria, especially *Pseudomonas aeruginosa*. Other chemicals such as caspofungin (Bink et al. 2012) and farnesol (Ramage et al. 2002) were shown to be active against the biofilms of *Candida albicans*. Lastly, antibiotics at sublethal concentrations were shown to inhibit biofilms, which is of interest, as these sublethal concentrations are less likely to induce the development of resistance (Balaji et al. 2013; Gilbert et al. 2002; Latimer et al. 2012).

Various microbial extracts (Bakkiyaraj and Pandian 2010; Bakkiyaraj et al. 2012; Nithya et al. 2010b, 2011; Nithya and Pandian 2010) and their secondary metabolites like usnic acid and atranorin (Pompilio et al. 2013), glycolipid biosurfactants (Kiran et al. 2010), phenylacetic acid (Musthafa et al. 2012b), ophiobolins (Arai et al. 2013), and piperazinedione (Musthafa et al. 2012a) were reported to have antibiofilm properties against bacterial and fungal pathogens. Apart from the microbial metabolites, enzymes were also shown to inhibit the

formation of biofilms. Alpha amylase produced by *Bacillus subtilis* (Kalpana et al. 2012), acylase produced by *B. pumilus* (Nithya et al. 2010a), alginate lyase (Lamppa and Griswold 2013), and protease produced by *P. aeruginosa* and actinomycetes (Park et al. 2012a, b) were also shown to have antibiofilm potential against human bacterial pathogens.

Numerous plants have been reported to display antibiofilm activities against bacterial and fungal pathogens. Cinnamaldehyde (Brackman et al. 2008), methyl eugenol (Packiavathy et al. 2012), casbane diterpene (Cardoso Sa et al. 2012), curcumin (Packiavathy et al. 2013), taxodione derivatives (Kuzma et al. 2012), gallic acid and ferulic acid (Borges et al. 2012), and ellagic acid (Sarabhai et al. 2013) are the notable plant products with potential antibiofilm activity.

The latest developments in the field of antibiofilm research employ novel agents like peptides (Amer et al. 2010; Choi and Lee 2012; Reymond et al. 2013; Zhang et al. 2010) and nanoparticles (Anghel et al. 2012; Hernandez-Delgadillo et al. 2012, 2013; Lellouche et al. 2012b; Durmus and Webster 2013; Martinez-Gutierrez et al. 2013; Sawant et al. 2013) as antibiofilm agents. The synthesis, properties, and the application of nanoparticles as antibiofilm agents will be discussed in detail in this chapter.

2 Properties and Synthesis of Nanoparticles

Among the antibiofilm technologies that have recently emerged, nanotechnology is one of the most promising. Nanotechnology can be defined as "a technology of engineering functional systems at molecular scale." Nanotechnology can also be defined as technology involving design, synthesis, and application of materials and devices whose size and shape have been engineered at nanoscale. Particles produced through nanotechnology are called "nanoparticles" and are typically sized less than 100 nm. Nanoparticles are highly reactive and preferred over other bioactive agents because of their higher surface area in contrast to their size. For example, 1 μg of particles of 1 nm^3 size have the same surface area as 1 g of particles of size 1 mm^3. Huge surface area of these nanoparticles facilitates their use as drug carriers.

Even though diverse chemicals like chitosan (Du et al. 2008), carboxymethyl chitosan (Zhao et al. 2013b), poly-gamma-glutamic acid (Liu et al. 2013b), cellulose (Raghavendra et al. 2013), zinc oxide (ZnO) (Dutta et al. 2013; Jones et al. 2008), magnesium fluoride (Lellouche et al. 2009, 2012b, c), polyethyleneimine (Beyth et al. 2010), hydroxyapatite (Evliyaoglu et al. 2011), fullerene (Patel et al. 2013), lipids (terpinen-4-ol) (Sun et al. 2012), and silica (Besinis et al. 2014; Li and Wang 2013) were shown to be useful, metals are the prime component of most nanoparticles. Derivatives of metals, like their oxides, form the base material for synthesis of many nanoparticles. Silver (Antony et al. 2013; Apte et al. 2013b; Besinis et al. 2014; Chernousova and Epple 2013; Jain and Pradeep 2005; Mohanty et al. 2012), gold (Annamalai et al. 2013; Geethalakshmi and

Sarada 2012; Khan et al. 2012; Naz et al. 2013; Pender et al. 2013; Ramamurthy et al. 2013), copper (Eshed et al. 2012; Kim et al. 2006; Pandiyarajan et al. 2013; Pramanik et al. 2012; Singh et al. 2013; Thekkae Padil and Cernik 2013), titanium (Besinis et al. 2014; Jayaseelan et al. 2013; Li et al. 2013), and iron (Das et al. 2013; Grumezescu et al. 2011; Leuba et al. 2013) are the predominant members of metal oxide nanoparticles and other metals like bismuth (Hernandez-Delgadillo et al. 2012, 2013) and cerium oxide (Shah et al. 2012) are other metal nanoparticles shown to possess bioactive potential.

Nanoparticles are synthesized either through a scale-up process, where atoms are grouped together, or a scale-down process, where larger molecules are minced to nanoscale. Irrespective of the methods used, synthesis of nanoparticles involves evaporation/dissolution, nucleation, and growth.

The synthesis of nanoparticles by scale-down or sizing-down processes can be achieved either by attrition or milling, followed by size-dependent grouping and selection. Scale-up processes can be broadly classified into three groups: gas phase fabrication; liquid phase fabrication; and biosynthesis or green synthesis of nanoparticles.

2.1 Gas or Vapor Phase Nanoparticle Fabrication

This process involves the evaporation of solid and liquid precursors to gaseous precursors followed by supersaturation, producing an intermediate product. Nucleation or condensation of these intermediate products results in primary particles. These primary particles, upon grain growth and agglomeration, produce nanoparticles and nanoclusters, respectively. Methods that employ gas phase fabrication are as follows:

1. Methods using solid precursors (Iskandar 2009)
    - Inert gas condensation
    - Pulsed laser ablation
    - Spark discharge generation
    - Ion sputtering
2. Methods using liquid or vapor precursors (Suciu et al. 2003)
    - Chemical vapor synthesis
    - Spray pyrolysis
    - Laser pyrolysis/photochemical synthesis
    - Thermal plasma synthesis
    - Flame synthesis
    - Flame spray pyrolysis
    - Low-temperature reactive synthesis

2.2 Liquid Phase Nanoparticle Fabrication

Liquid phase fabrication involves wet chemistry and the general process includes the surface reaction of solid and liquid precursors to produce corresponding intermediate products. Such intermediate products are converted to primary particles either by nucleation or condensation similar to gas phase fabrication, followed by growth or agglomeration to produce nanoparticles or nanoclusters, respectively. Methods that employ liquid phase fabrication are:

1. Co-precipitation (Murray et al. 2000)
2. Solvothermal methods (Yang et al. 2006)
3. Sol–gel methods (Yu et al. 2004)
4. Synthesis in structure media (e.g., Microemulsion) (Capek 2004)
5. Microwave synthesis (Tsuji et al. 2005)
6. Sonochemical synthesis (Zhang and Yu 2003)

2.3 Biological Synthesis of Nanoparticles

Synthesis of nanoparticles catalyzed by bacteria or fungi or their products is of considerable interest as it employs cleaner and greener technology. Numerous fungi and bacteria have been utilized for the bioconversion of raw chemicals into nanoparticles. For instance, the ability of the marine yeast *Yarrowia lipolytica* to catalyze the synthesis of gold nanoparticles has been reported (Agnihotri et al. 2009; Apte et al. 2013a, b). Biosynthesis of silver, gold, and bimetallic nanoparticles by fungi like *Phanerochaete chrysosporium*, *Penicillium* sp., and *Neurospora crassa* has also been reported (Castro-Longoria et al. 2011; Du et al. 2010; Vigneshwaran et al. 2006). Similarly, the synthesis of silver nanoparticles with antimicrobial potential by psychrophilic bacteria such as *Pseudomonas antarctica* and *Arthrobacter kerguelensis* has also been reported (Shivaji et al. 2011). *Lactobacillus fermentum* (Sintubin et al. 2009) and *Shewanella oneidensis* (Suresh et al. 2010) were also shown to catalyze the production of silver nanoparticles with antimicrobial potential.

Though there are numerous reports on the microbe-mediated synthesis of nanoparticles, very few studies have described the biomolecules involved in this synthesis. For example, nitrate reductase along with a protein from *Aspergillus niger* and nitrate reductase along with rhamnolipids from *P. aeruginosa* were shown to be indispensable for the synthesis of nanoparticles (Gade et al. 2008; Kumar and Mamidyala 2011). Similarly, the role of cell-bound melanin produced by the yeast *Y. lipolytica* and certain proteins produced by marine fungi *A. tubingensis* and *Bionectria ochroleuca* in the synthesis of silver nanoparticles with antibiofilm activity have been reported recently (Apte et al. 2013a, b; Rodrigues et al. 2013).

3 Diverse Applications of Nanoparticles

Nanoparticles or nanomaterials in general have diverse applications in various fields.

3.1 Industrial Applications

Many microelectronic instruments such as transistors have adapted nanotechnology (Thompson and Parthasarathy 2006). Carbon nanotubes are reported to be the nanoscale alternatives to conventional semiconductor crystals because of their diverse electronic properties from metallic to semiconducting (Jacoby 2002) or superconducting (Cristina and Kevin 2005). Carbon nanotubes have been shown to be useful in making low-voltage field-emission displays (Carey 2003). Nanomaterials like aerogel intercalation electrode materials, nanocrystalline alloys, nanosized composite materials, carbon nanotubes, and nanosized transition metal oxides have shown promise in the development of lithium-ion batteries with increased capacity and lifecycle over their conventional counterparts (Liu et al. 2006a; Scott et al. 2011).

Nanocrystalline materials synthesized by the sol–gel technique exhibit foam-like structures called "aerogel" which find application as insulation material in industries because of their negligible thermal conductivity (Hrubesh and Poco 1995). Paints that have incorporated nanoparticles (Titanium oxide) demonstrate enhanced mechanical properties, such as scratch resistance. For example, the wear resistance of paint-nanocomposite coatings is claimed to be ten times higher than that of conventional acrylic paints (Mochizuki et al. 2013).

In the automobile industry, nanoparticles of carbon black act as filler in the polymer matrix of tires and are used for mechanical reinforcement. Nanocomposites containing the flakes of clay and plastics and nanosized clay are used in manufacturing the exteriors of cars with superior properties like scratch resistance compared to traditional materials.

Nanoparticles have found their way into the food industry due to their antimicrobial properties. For example, silver-montmorillonite (Ag-MMT) nanoparticles were used in the prevention of food spoilage (Costa et al. 2011). In addition to preventing the growth of food-spoiling microbes, Ag-MMT nanoparticles also preserved color, odor, and firmness of the food (Costa et al. 2011).

Nanoparticles also have potential in controlling pollution because of their ability to catalyze the conversion of toxic gases (carbon monoxide and nitrogen oxide) from the exhaust of vehicles and power generators. Iron nanoparticles, along with palladium, converted detrimental products in groundwater to inert or less harmful products (He and Zhao 2005). The nanoparticles were also shown to be effective in removing organic chlorine (a carcinogen) from water contaminated with the chlorine-based organic solvents (used in dry cleaners).

3.2 Nanoparticles in Biotechnology and Medicine

Carbon nanotubes have been used as probe tips in atomic force microscopy (AFM) which is used for high-resolution imaging of nucleic acids, immunoglobulins, etc. (Hafner et al. 2001). Molecular recognition and the chemical forces between the interacting molecules can be studied by attaching AFM tips bearing these biomolecules (Hafner et al. 2001).

Nanofiber scaffolds have been employed in the regeneration of cells and organs. Experiments on a hamster with a detached optic tract demonstrated that a peptide nanofiber scaffold could facilitate the regeneration of axonal tissue (Ellis-Behnke et al. 2006). Titanium dioxide and zinc oxide are used in sunscreens and cosmetics to absorb and reflect UV light.

Nanotube membranes can act as channels for highly selective transport of molecules and ions between solutions that are present on both sides of the membrane (Jirage et al. 1997). For instance, membranes containing nanotubes with small inner dimensions (less than 1 nm) were useful for the separation of small molecules on the basis of molecular size, while the nanotubes with larger inner diameters (20–60 nm) were used to separate proteins (Martin and Kohli 2003).

The ability of nanoparticles to target and penetrate specific cells and organs has also been explored in nanomedicine. Nanospheres made of biodegradable (facilitating timely release) polymers and drugs have potential applications in acidic microenvironments as in the case of tumor tissues or sites of inflammation (Kamaly et al. 2012). Nanoparticles acted as drug carriers for the targeted release of a conjugate containing chlorotoxin (a peptide that selectively binds to glioblastoma cells) and liposomes encapsulating antisense oligonucleotides or small interfering RNAs for effective treatment of glioblastoma (Costa et al. 2013). Similarly, numerous other studies have independently demonstrated the utility of nanoparticles as drug carriers in different tumor types (Amoozgar et al. 2013; Leifert et al. 2013; Liu et al. 2013a; Shi et al. 2013; Vivek et al. 2013).

In addition, surface-functionalized nanoparticles can be used to infuse cell membranes at a much higher level than nanoparticles without a functionalized surface, which can be employed for transfer of genetic material into living cells (Lewin et al. 2000). Silica nanospheres coated with ammonium groups (cation) can bind to DNA (anion) through electrostatic interactions, which could be used to deliver the latter into the cells (Kneuer et al. 2000).

Nanospheres can act as carriers for antigens and toxoids for potential use in vaccination. Studies involving antigen-coated polystyrene nanospheres as vaccine carriers targeting human dendritic cells have been under trial for nasal vaccination (Matsusaki et al. 2005). Studies have also unveiled the potential of nanoparticles in the diagnosis and treatment of various cancers. For instance, a study by Yin et al. (2013) showed enhanced anticancer action of curcumin upon coupling it with nanoparticles made from methoxy poly(ethylene glycol)-polycaprolactone (PCL) block copolymers (Yin et al. 2013). Similarly, the silver nanoparticles were shown to inhibit lung cancer cells in a concentration-dependent manner

(Sankar et al. 2013). Iron nanoparticles coupled with high-resolution MRI detected lymph node metastases in patients with prostate cancer at a stage undetectable by any other method (Harisinghani et al. 2003) and the gold nanoparticles were employed for the accurate detection of matriptase—a cancer biomarker protein overexpressed in all types of cancer (Deng et al. 2013). Lastly, nanoparticles made of compounds with oxygen vacancies (CeO_2 and Y_2O_3) (Schubert et al. 2006) have been demonstrated to possess neuroprotective and anti-apoptotic properties.

3.3 Antimicrobial Activity of Nanoparticles

Nanoparticles have been considered to be some of the most effectual bioactive agents mainly because of their large surface area to volume ratio (Hamouda 2012). Nanopowders possess antimicrobial properties against various bacterial, fungal and viral human pathogens (Koper et al. 2002; Bosi et al. 2003) and can rapidly kill bacterial cells (90 % in 1 h). The antibacterial properties of silver and titanium dioxide nanoparticles have been assessed as coatings for surgical masks (Li et al. 2006), in addition to many other clinical uses.

Nanoparticles shown to have antimicrobial effects include silver (Lara et al. 2010; Lok et al. 2006), titanium dioxide (Li et al. 2006), fullerenes (Bosi et al. 2003), zinc oxide (Brayner et al. 2006), and magnesium fluoride (Lellouche et al. 2012c). The antibacterial activity of fullerenes was reported against *Escherichia coli*, Salmonella and *Streptococcus* spp. (Bosi et al. 2003). The ability of zinc oxide nanoparticles to disturb the membrane permeability of *E. coli* has also been reported (Brayner et al. 2006). The wide spectrum antimicrobial activity of silver nanoparticles has been attributed to their ability to destabilize the bacterial outer membrane and deplete adenosine triphosphate (principal form of energy) in bacteria (Lara et al. 2010; Lok et al. 2006).

Fullerenes have also been shown to have neuroprotective, anti-apoptotic, and anti-HIV activities (Bosi et al. 2003). Size-dependent interactions of silver nanoparticles and HIV-1 virus were reported, which resulted in the inhibition of host–viral interactions (Elechiguerra et al. 2005). Numerous other studies have demonstrated the antimicrobial potential of various nanoparticles and drug–nanoparticle conjugates against bacterial, fungal, and viral pathogens (Zheng et al. 2013; Zhao et al. 2013a; Zhang et al. 2013c; Xiong et al. 2013; Westendorf 2013; Wang and Lim 2013; Wang et al. 2013; Vidic et al. 2013; Tavassoli Hojati et al. 2013; Su et al. 2013; Shimizu et al. 2013; Mohanty et al. 2012; Mallick et al. 2012; Lellouche et al. 2012a; Costa et al. 2011; Mukhopadhyay et al. 2010; Huda et al. 2010; Sanpui et al. 2008; Pinto et al. 2013; Hernandez-Delgadillo et al. 2013; Monteiro et al. 2012; Khan et al. 2012; Lara et al. 2010).

4 Nanoparticles as Antibiofilm Agents

The application of nanoparticles is an emerging area of antibiofilm or antipathogenic research. Nanoparticles are preferred over other agents due to their acute ability to penetrate EPS and cell membranes. Nanoparticles were found to be efficient drug carriers, effectively transporting drugs across the biofilm matrix. Silver, iron and zinc nanoparticles have received the most attention as antibiofilm agents. Silver nanoparticles are the predominant ones with antibiofilm activity against Gram-positive bacteria like *S. aureus*, *S. epidermidis*, *E. faecalis*, and *Streptococcus mutans*; Gram-negative bacteria like *P. aeruginosa*, *Salmonella paratyphi*, *E. coli*, and *Acinetobacter baumannii*; and fungal pathogens like *C. albicans* and *C. glabrata*. Details of nanoparticles with antibiofilm activities, along with their target pathogens, are given in Table 1.

The use of nanoparticles in combination with other antibiotics or drugs was found to have superior action than when alone. Chitosan nanoparticles loaded with Tamoxifen were effective in controlling tumor development in breast cancer cell lines (Vivek et al. 2013). Similarly, the side effects of daunorubicin were reduced significantly when combined with titanium oxide nanoparticles, which increased the target specificity and anticancer activity in leukemia cells (Zhang et al. 2012). Silver nanoparticles in combination with conventional antibiotics like ampicillin, chloramphenicol, and kanamycin have shown antibiofilm activity against Gram-positive and negative bacterial pathogens including *E. faecium*, *S. aureus*, *E. coli*, and *P. aeruginosa* (Hwang et al. 2012).

5 Demerits of Nanoparticles

Even though nanoparticles have historically been considered inert, they are actually highly reactive. The large surface area of nanoparticles can be both a pro and a con to their application in biology. Nanoparticles are commonly found in dust and aerosols. Inhaled nanoparticles deposited in the lungs are cleared through host processes such as mucociliary escalation into the gastrointestinal tract (from where they are eliminated through the feces) (Semmler et al. 2004), lymphatic system (Liu et al. 2006b), and circulatory systems (Oberdorster et al. 2005). Failure to clear these nanoparticles results in accumulation in lungs, subsequently increasing the risk of lung cancer (Borm et al. 2004). Accumulation of nanoparticles in lungs also elicits an inflammatory response that damages host tissues (Oberdorster et al. 1994). Adverse effects to nanoparticles include impaired phagocytosis, inflammation, epithelial cell proliferation followed by fibrosis, emphysema, and the initiation of tumors (Ferin 1994; Oberdorster et al. 1994; Nikula et al. 1995; Dasenbrock et al. 1996; Driscoll et al. 1996; Borm et al. 2004).

Inhalation of nanoparticles can also result in immune suppression and reduction in the ability of the immune system to combat infections (Lucarelli et al. 2004).

Table 1 Antibiofilm activity of nanoparticles and their target pathogens

Nanoparticle	Target organism	References
Silver nanoparticles	*S. paratyphi*, *P. aeruginosa*, *S. epidermidis*	Apte et al. (2013b), Kalishwaralal et al. (2010)
Bismuth oxide aqueous colloidal nanoparticles	*C. albicans*, *S. mutans*	Hernandez-Delgadillo et al. (2012, 2013)
Nano-oil formulation from *Mentha piperita* L.	*Staphylococcus* sp.	Anghel and Grumezescu (2013)
Nanoemulsion (detergent, oil, and water) in combination with cetylpyridinium chloride	*A. baumannii*	Hwang et al. (2013)
Silver and gold incorporated polyurethane, polycaprolactam, polycarbonate, and polymethylmethacrylate	*E. coli*	Sawant et al. (2013)
Silver nanoparticles in combination with nystatin and chlorhexidine	*C. albicans*, *C. glabrata*	Monteiro et al. (2012, 2013)
Silver nanoparticle and 12-methacryloyloxydodecylpyridinium bromide (MDPB)	Dental plaque microcosm biofilms	Zhang et al. (2013a, b)
Zinc	*Actinobacillus pleuropneumoniae*, *S. typhimurium*, *Haemophilus parasuis*, *E. coli*, *S. aureus*, *S. suis*	Wu et al. (2013)
Magnetite nanoparticles	*C. albicans*	Anghel et al. (2012)
Eugenia carryophyllata essential oil stabilized by iron oxide/oleic acid core/shell nanostructures	*S. aureus*	Grumezescu et al. (2011, 2012)
Zinc and copper oxide nanoparticles	*S. mutans*	Eshed et al. (2012)
Zerovalent bismuth nanoparticle	*S. mutans*	Hernandez-Delgadillo et al. (2012)
Silver nanoparticles in combination with ampicillin, chloramphenicol, and kanamycin	*Enterococcus faecium*, *S. aureus*, *E. coli*, *P. aeruginosa*	Hwang et al. (2012)
Dextran sulfate nanoparticle complex containing ofloxacin and levofloxacin	*P. aeruginosa*	Cheow and Hadinoto (2012)
PEG-stabilized lipid nanoparticles loaded with terpinen-4-ol	*C. albicans*	Sun et al. (2012)
Magnesium fluoride nanoparticles	*S. aureus*, *E. coli*	Lellouche et al. (2009, 2012b, c)
Yttrium fluoride nanoparticles	*S. aureus*, *E. coli*	Lellouche et al. (2012a)
Iron oxide/oleic acid in combination with essential oil from *Rosmarinus officinalis*	*C. albicans*, *C. tropicalis*	Chifiriuc et al. (2012)
Gold nanoparticles and methylene blue	*C. albicans*	Khan et al. (2012)
Starch-stabilized silver nanoparticles	*S. aureus*, *P. aeruginosa*	Mohanty et al. (2012)

(continued)

Table 1 (continued)

Nanoparticle	Target organism	References
Iron oxide–oleic acid nanofluid	*S. aureus*	Grumezescu et al. (2011)
Chitosan, zinc oxide, nitric oxide nanoparticles	*E. faecalis*	Shrestha et al. (2010)
Quaternary ammonium polyethylenimine nanoparticles	Oral biofilms	Beyth et al. (2010)
Zinc oxide nanoparticles, chitosan nanoparticles, and combination of both	*E. faecalis*	Kishen et al. (2008)
Polyurethane nanocomposite	*S. epidermidis*	Styan et al. (2007)

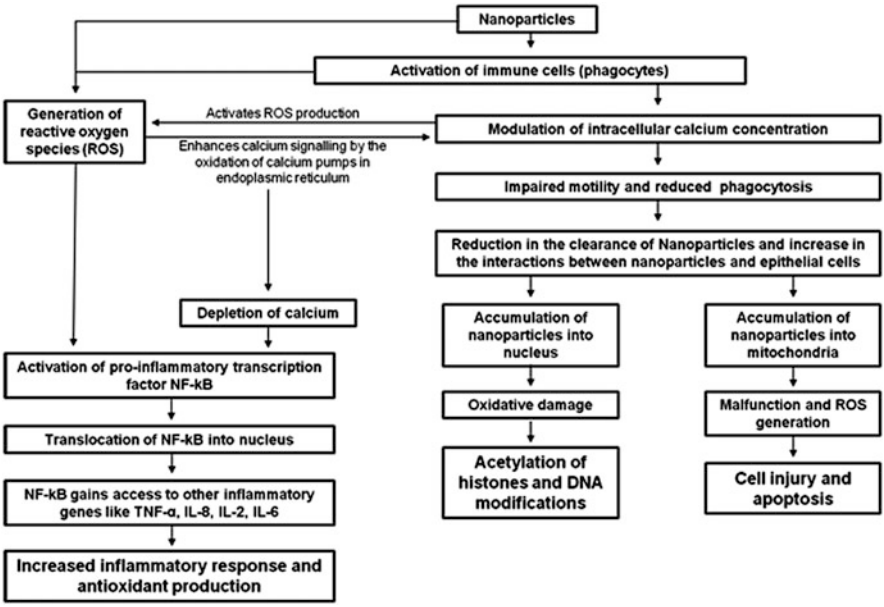

Fig. 1 Molecular mechanisms involved in nanoparticle-induced cellular toxicity (adopted and modified from Buzea et al. 2007)

Exposure to nanoparticles like zirconium dioxide (ZrO_2) induces overexpression of viral receptors and in turn results in hyper-reaction of the immune system and subsequent unwarranted inflammation (Lucarelli et al. 2004). In vivo and in vitro studies have shown the ability of nanoparticles (fullerenes, carbon nanotubes, quantum dots, and automobile exhaust) to initiate the production of reactive oxygen species (ROS) (Oberdorster et al. 2005), which has been shown to play a key role in cell damage by peroxidizing lipids, damaging proteins and nucleic acids, interfering with signaling functions, and modulating gene expression (Brown et al. 2004; Risom et al. 2005; Peters et al. 2006; Mehta et al. 2008). Malfunction of mitochondria has also been observed upon nanoparticle treatment as they effectively enter these organelles and contribute to oxidative stress and damage (Li et al. 2003; Xia et al. 2006; Sioutas et al. 2005). There is also evidence of the adverse effects

(appearance of thrombi) of nanoparticles on the cardiovascular system (Schulz et al. 2005; Nemmar et al. 2002; Vermylen et al. 2005; Hoet et al. 2004). Uptake of nanoparticles through skin results in their accumulation in the lymphatic system causing podoconiosis (Corachan 1988; Blundell et al. 1989) and Kaposi's sarcoma (Montella et al. 1997; Mott et al. 2002). Molecular mechanisms involved in nanoparticle-mediated cellular toxicity are schematically represented (Fig. 1).

6 Conclusions

Nanotechnology is a nascent field of science with promising potential in many fields including physics, chemistry, biology, pharmacology, and medicine. As discussed in this chapter, nanoparticles can be our friend or foe. Although there are reports which state nanoparticles are toxic, there is always the potential for improvement and development of safe and effective novel nanoparticles or nanocomposites. The utility of nanoparticles as drug carriers appears to be an important tool for targeted tumor therapy, and enhancing the efficacy of drugs could be another attractive application for nanomaterials. Even though the use of nanoparticles in vivo is debatable for now, their use on inanimate objects is effective. Without any doubt, the future will witness increasing use of nanoparticles in many fields, hopefully for the improvement of mankind.

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