Chapter 5
Antimicrobial Activity of Nanomaterials

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Contents

Abstract The World Health Organization reports that millions of deaths occurring worldwide are because of infectious diseases caused by bacteria, viruses, fungi and parasites. The existing therapeutics is not adequate enough to fight against these diseases and their prolonged uses have led to the development of drug-resistant strains which are even more difficult to control. Hence, the need for an alternative approach is growing. Development of nanotechnology, especially nanostructured particles and formulations, is providing new opportunities to combat these infectious diseases more effectively. Nanomaterials have unique physicochemical

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properties like tuneable size, large surface to volume ratio, high reactivity, biocompatibility and functionalizable surface area. These properties are applied to facilitate the applications of antimicrobial drugs, thereby overcoming some of the limitations of traditional antimicrobial therapeutics. Moreover, the therapeutic effect and drug delivery approach of these nanomaterials have emerged as an innovative and promising alternative that enhance therapeutic effectiveness against pathogenic microorganisms and minimize undesirable side effects of the drugs. In order to enumerate the antimicrobial effect of these nanomaterials, this chapter is designed to discuss commonly used nanomaterials such as lipid vesicle dendrimers, polymeric and inorganic nanoparticles, carbon nanostructures, quantum dots, electrospun nanofibres, nanoclays, etc. against infectious diseases.

Keywords Antimicrobial · Dendrimers · Lipid vesicles · Nanoclays · Nanofibers · Quantum dots

5.1 Introduction

Microorganisms, as the name suggest, are microscopic living organisms that are visible with the help of aided microscopic devices. They have inhabited on earth for more than 3.5 billion years and are regarded as the first form of life on the planet. Most of these microorganisms are unicellular (single-celled) such as bacteria but few are multicellular such as algae and fungi. They survive in different environments and their habitat ranges from ice cold climate to hot springs, deserts to marshy lands and skin surfaces to the gut. Though they are omnipresent, their presence in the environment may be beneficial or harmful to others. The association of useful microorganisms such as bacteria and fungi with humans is as old as the civilization. Their important role in different nutrient cycles, decomposition of harmful chemical pollutants and wastes, fermentation, digestion of food and protection from harmful microbes in the body, production of vaccines and antibiotics, genetic engineering and biotechnology is effectively utilized in different applications for the benefit of humans (Tortora et al. 2004). Similar is the case with pathogenic (harmful) microorganisms that cause infections and diseases such as dysentery, diarrhoea, tuberculosis and cholera in humans. These pathogenic microorganisms have received significant attention due to their harmful effects leading to suffering and death in humans. In 2015, the World Health Organization (WHO) estimated that 3.2 million deaths worldwide were due to respiratory infections and 1.4 million deaths due to diarrhoeal diseases and tuberculosis each (WHO 2015). The report briefly showed the magnitude of threat these pathogenic microbes are causing to the human population and how important it is to control their growth through therapeutic approaches. Moreover, the emergence of antimicrobial resistance (AMR) strains of bacteria, fungi and parasites is becoming a serious threat to public health leading to disease severity and their treatment (Roca et al. 2015). Globally, it is found that around

700,000 deaths occur each year due to resistance to antimicrobial drugs by emerging strains of mutant microorganisms. It is estimated that such AMR strains of organisms would be accountable for the death of around 10 million people worldwide by 2050 (Robinson et al. 2016). In order to conquer deaths caused by infectious diseases and avoid the emergence of any resistant strains, researchers worldwide are looking for alternatives that can be used against a broad range of microbial populations. New alternatives to antibiotics have been identified till date including antibodies, probiotics, bacteriophages, vaccines and antibiofilm peptides that can be used against infectious diseases (Czaplewski et al. 2016; François et al. 2016; Ploegmakers et al. 2017; Wang et al. 2016). In addition to these, various nanostructures and nanoformulations with existing drugs were found to be effective against different infectious diseases (Malmsten 2014; Karaman et al. 2017; Raghunath and Perumal 2017). These nanostructures interact physiochemically with the cells and cellular organelles for effective therapeutic treatment (Nel et al. 2009). These physiochemical interactions lead to reorientation of the metabolic pathways inside the cells disturbing the biological mechanisms like protein folding, membrane dynamics, enzyme catalysis and DNA replication. which inhibit microbial growth (Moyano and Rotello 2011; Dewan et al. 2014). Additionally, the generation of reactive oxygen species (ROS), metal-ion release, nanoparticle internalization into cells and direct mechanical destruction of the cell wall and/or membrane by the nanomaterials contribute to the disruption/deaths of microorganisms (Pelgrift and Friedman 2013). Irrespective of the mechanism of microbial cell death, nanomaterials are giving hopes for an alternative to age-old therapeutic agents used till date. The use of different nanostructures such as liposomes, dendrimers, quantum dots, nanoclays and other nanoparticles serves a dual purpose against infectious diseases: firstly, they themselves possess therapeutic properties that inhibit the proliferation of microbial growth and secondly, they aid drug delivery by transporting drugs to the target site of action which otherwise was not possible directly. In this chapter, the therapeutic potential of nanomaterials such as lipid vesicles, dendrimers, polymeric and inorganic nanoparticles, nanofibres, nanoclays, quantum dots and carbon nanomaterials is discussed along with brief description of the diseases caused by microbes such as bacteria, fungi, protozoa and viruses and their existing therapeutics.

5.2 Microbial Diseases and Their Existing Therapeutics

Most people link microorganisms as disease-causing agents, but not all microorganisms are harmful (Tortora et al. 2004). The beneficial processes of microbes include decomposition of dead plants and animals; protection against harmful pathogens by altering the pH, acidity level, releasing toxins and regulating and stimulating the immune system (Calder and Field 2002; Reid and Burton 2002). On the contrary,

harmful microbes cause diseases in humans by defeating the immune system and eliciting their harmful effect. The mechanisms followed by these microorganisms to cause illness in humans are either through rapid multiplication inside the host that disrupts the normal function of the organs or destruction of metabolic machinery of the cells/tissues by the production of toxins (Fauci 2004). Several microorganisms responsible for causing diseases in humans are species of bacteria, fungi, protozoa and viruses that enter the body by contact (infected skin, mucous membranes and body fluids), contaminated food and water, blood and vectors such as fleas, mites, ticks and mosquitoes. Common diseases such as pneumonia, bronchitis, whooping cough and tuberculosis (affecting the respiratory tract); typhoid fever, cholera, botulism, peptic ulcer, dysentery and food poisoning (affecting gastrointestinal tract); urinary tract infections; and skin infections are mostly caused by bacterial species of *Streptococcus*, *Staphylococcus*, *Enterococcus*, *Haemophilus*, *Enterobacter*, *Mycobacterium*, etc. Moreover, diseases such as aspergillosis, candidiasis, ringworm and some skin infections are caused by fungi species, namely, *Aspergillus, Candida, Tinea and Cryptococcus*, whereas malaria is caused by a protozoon, *Plasmodium*. However, infections like common cold, influenza, meningitis, encephalitis, chikungunya, chicken pox and AIDS are caused by viruses (Goering et al. 2018).

In order to combat any infection, the defence mechanism of our body is immediately elicited. It is well known that the T-cells are responsible for antimicrobial activity by producing lymphokines at the site of infection (Reinhardt et al. 2001). Failure of this internal defence system against microorganisms leads to infection, and then therapeutic treatment is required. Conventionally, the use of plant extracts, aromatic herbs, essential oils, etc. occurring naturally had been in use as antimicrobial agents to treat a number of infectious diseases around the world, but the discovery of antibiotics leads to a new therapeutic treatment approach (Khan et al. 2009; Solórzano-Santos and Miranda-Novales, 2012). Antibiotics are metabolites produced by certain microorganisms naturally or their semisynthetic derivatives, which inhibit the growth of certain other microorganisms. The first discovered antibiotic penicillin produced by a fungus *Penicillium chrysogenum* was extensively used during World War II to control the spread of infectious diseases. Since then, several other antibiotics, namely, actinomycin, erythromycin, rifamycin, streptomycin, tetracycline and vancomycin produced by species *Streptomyces*; bacitracin and polymyxin by *Bacillus*; and cephalosporin by *Cephalosporium*, are till date being used for the treatment of different infections caused by bacteria (Finch et al. 2010). In cases of fungal infections, the treatment regimen is often difficult to formulate because human cells, also being eukaryotic are susceptible to harm. In order to circumvent this, antibiotics such as amphotericin B; nystatin; griseofulvin in combination with synthetic imidazoles, triazoles and their derivatives; and pyrimidine analogues are commonly used (Denning and Hope 2010). However, antiviral drugs such as acetaminophen and ibuprofen against common cold and flu; acyclovir, valaciclovir, etc. against herpes virus; human recombinant interferon alpha and PEGylated interferon alpha against hepatitis B; and zidovudine, didanosine, tenofovir disoproxil, etc. against HIV hinder the ability of these viruses to reproduce and

control their spread (De Clercq 2004). In addition to these, combined drug therapies are used to treat diseases caused by protozoa, for example, metronidazole and iodoquinol against amoebiasis; amphotericin B and chlorpromazine against amoebic meningoencephalitis; artemisinin and metal-based therapy against malaria, trypanosomiasis and leishmaniasis (Sayang et al. 2009; Navarro et al. 2010).

Although good medical progress was made during the last century in developing antibiotics and chemically derived synthetic analogues, infections still remain a major public health problem worldwide. This problem is further aggravated by the emergence of antimicrobial resistance (AMR) strains that occurred due to prolonged exposure to similar drugs, administered in different ways and diseases worldwide. Though the mechanism of development of AMR is not fully understood, several mechanisms have been described, including the acquisition of antibiotic resistance genes via the transfer of genetic elements or mutations leading to altered expression of redox-active proteins, altered drug metabolism either by substitution or degradation, changing the chemical composition of cell wall leading to decreased permeability of drugs, etc. (Yelin and Kishony 2018), as well as the formation of biofilms (Peng et al. 2017). The well-known mechanism of development of AMR strains (schematically represented in Fig. 5.1) includes: (i) the formation of modified cell walls that restrict the penetration of drugs into the cell, (ii) production of chemically active molecules that conjugate with the drug molecules and render them inactive, (iii) increased channel activity that pumps out the drug molecules and (iv) production of modified binding receptors that are unable to bind to the drug molecules.

The emergence of AMR strains of microorganisms is becoming a serious threat to human population in the twenty-first century which demands for a new treatment regimen so that millions of deaths can be avoided in the future. This is possible only through the synthesis or discovery of active novel molecules and their encapsulation within nanomaterials so that the drug can reach the cellular organelles where pathogens reside and kill the pathogens without harming the patients (Ogawa et al. 2018).

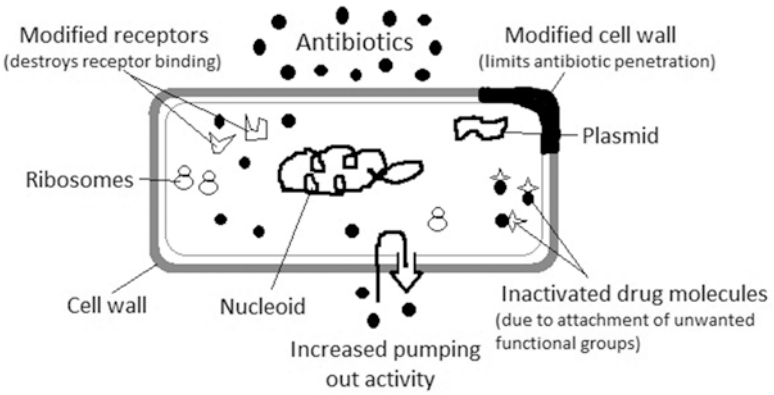

Fig. 5.1 Mechanism of antimicrobial resistance. (Adopted from Singh et al. 2014)

5.3 Nanostructured Materials as Antimicrobial Agents

Nanostructured materials are seen as medical alternatives to antibiotics due to the capability to tailor them for specific diseases and site-specific targeted delivery. It is obvious that for pharmaceutical agents to render their therapeutic effect, the primary targets must be within cells and tissues so that selective subcellular delivery is likely to have greater benefit. Several organic and inorganic nanomaterials are currently in clinical and preclinical stages that have potential therapeutic effects. The nanomaterials with their noble properties such as size, surface to volume ratio, reactivity, biocompatibility and tunability offer biologically active domain for site-specific targeting, drug delivery, biocompatible coatings, etc. which can be engineered for healthcare applications (Fig. 5.2). Most engineered nanomaterials acting as drug delivery system and as therapeutic agents against infectious diseases are liposomes, dendrimers, polymeric nanoparticles, carbon nanostructures, quantum dots, electrospun nanofibres, nanoribbons, core-shell nanoparticles, etc. and are discussed in the following sections.

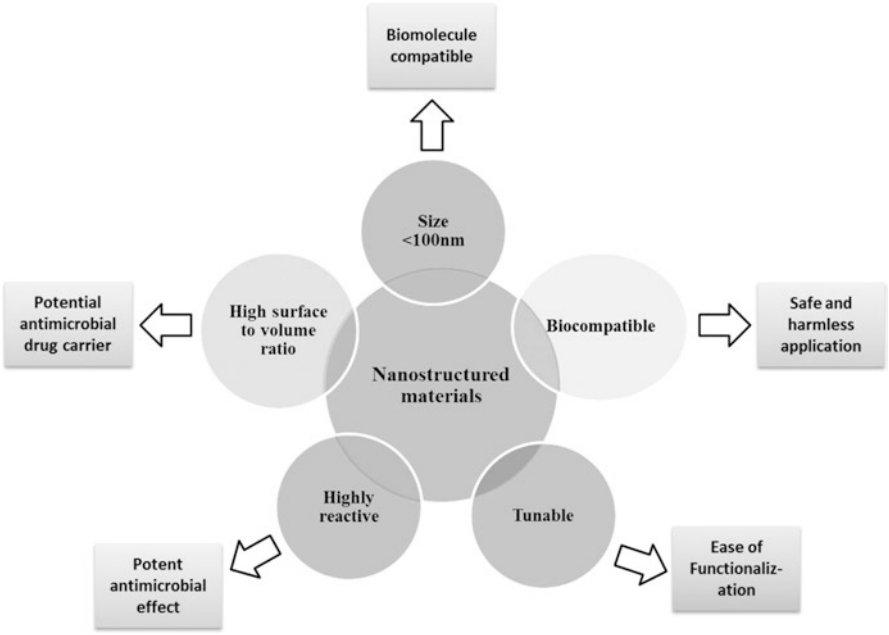

Fig. 5.2 Properties of nanostructured materials that make it potent antimicrobial agents

5.3.1 *Lipid Vesicles*

Lipid vesicles are composed of either mono- or bilayers of phospholipids with size ranging between 50 and 100 nm. The bilayer structures of phospholipids are known as liposomes and the monolayered ones are called micelles, whereas solid lipid nanoparticles (SLNs) are composed of a solid lipid core encapsulated with drugs and the nanocapsules consist of a liquid core with shell-type surface (Fig. 5.3).

The structural morphology of these lipid vesicles enables them to encapsulate a wide variety of hydrophilic and hydrophobic diagnostic or therapeutic agents, providing a good drug payload per particle and protecting the encapsulated drugs from metabolic processes. It is important to note that drug entrapped in these vesicles is bioavailable with or without stimulus such as pH and temperature. Moreover, the ability of accumulated lipid vesicles to increase the local bioavailable drug concentrations and their therapeutic outcome can only be enhanced when the rate of release of entrapped drug from these nanostructures is optimized (Johnston et al. 2006).

Conventional vesicles suffered drawbacks because of their rapid degradation following plasma protein adsorption. The next generation of these vesicles were designed to overcome this drawback by coating the surface with polymer derivatives such as polyethylene glycol (PEG) or carbohydrates. These sterically stable nanostructures have been shown to favourably work as drug delivery vehicles that withstand the metabolic processes and perform drug release in a controlled manner (Torchilin 2005). The mechanism of drug delivery using these lipid vesicles into the cell is performed in stages (Fig. 5.4); in the first stage, the nanovesicle-cell interaction occurs where they nonspecifically or specifically bind to the cell surface. Nonspecific adsorption occurs by simply an electrostatic and/or hydrophobic interaction between the two, while specific adsorption is a receptor-ligand or an antigen-antibody interaction between the two surfaces of the cell and the nanovesicle. Irrespective of whether the binding is specific or nonspecific, the nanovesicle is internalized into the cell by endocytosis. This is followed by the enzymatic digestion of the liposome in the intracellular compartment such as endosome, phagosome or acidosome, accompanied by the intracellular distribution of drugs to the cytosol (Daraee et al. 2016).

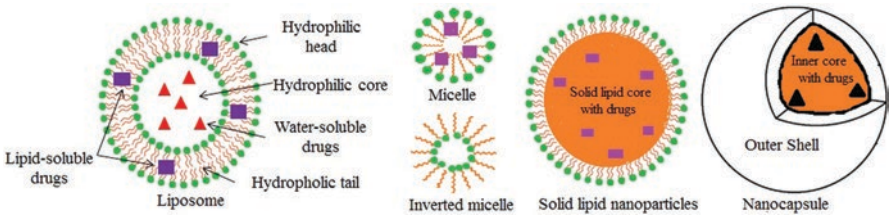

Fig. 5.3 Structure of lipid vesicles such as liposomes, micelle, solid lipid nanoparticles and nanocapsules containing entrapped drugs

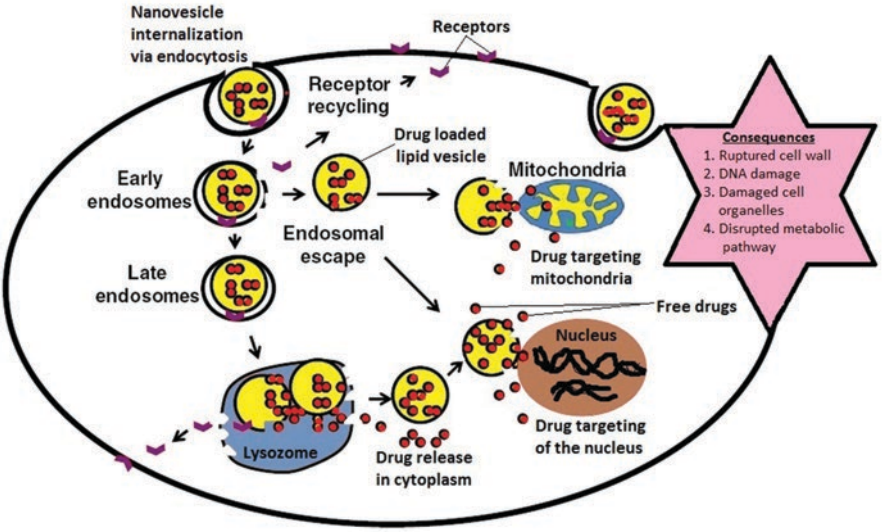

Fig. 5.4 Mechanism of drug delivery using nanovesicles with possible causes of microbial cell death. (Adopted from Çağdaş et al. 2014)

Liposomes were the first vesicular structure to be explored by encapsulating antibiotics and bioactive molecules to increase the therapeutic dose of the formulation, circulation time and bioavailability as compared to the free drug (Pinto-Alphandary et al. 2000; Barratt 2003). Mikasome, an amikacin liposomal formulation, was found to be more potent than the free drug against murine tuberculosis (Donald et al. 2001). Similarly, pulmonary administration of solid lipid nanoparticles containing rifabutin was reported to enhance antibacterial activity of *Mycobacterium tuberculosis* in a murine model (Gaspar et al. 2017). Improved bioavailability of kaempferol, a flavonoid compound, was achieved when loaded into lecithin/chitosan nanoparticles that proved to be potent against a pathogenic fungus *Fusarium oxysporum* (Ilk et al. 2017). Additionally, liposomes loaded with antibiotics have demonstrated excellent transportation capability and severalfold increase in potency in both in vitro and in vivo studies against *Pseudomonas, Salmonella*, *Streptococcus* and others (Pushparaj Selvadoss et al. 2018; Lakshminarayanan et al. 2018). Similar drug transportation potential was also seen in other lipid-based vesicular structures; i.e., dehydroascorbic acid (DHA)-coupled polymeric nanomicelles encapsulating itraconazole were effectively transported across the blood-brain barrier that showed high efficacy in a murine model of *Cryptococcus neoformans* infection of the central nervous system (Shao et al. 2015). The enrofloxacin-loaded docosanoic acid solid lipid nanoparticles with different physicochemical properties were developed to enhance intracellular activity against *Salmonella* and were considered to be a promising drug carrier (Xie et al. 2017). The antibiofilm activity of liposomal levofloxacin and lysozyme improved severalfold against lung infection caused by *S. aureus* in rats (Gupta et al. 2018). Additionally, lipid nanocapsule loaded with

antipsychotic agents such as chlorpromazine and thioridazine improved its overall uptake in bacteria and effectively inhibited proliferation of gram-positive *S. aureus* and gram-negative *E. coli*, *P. aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter baumannii* bacteria *in vitro* (Nehme et al. 2018).

Liposomes loaded with bioactive lipids, cinnamon oil, chitosan, peptides, etc. have been found to be effective in different strains of bacterial populations along with those of resistant strains (Cui et al. 2016; Poerio et al. 2017; Pu and Tang, 2017). Essential oils, such as eucalyptus or rosemary oils, loaded with solid lipid nanoparticles were able to promote wound healing in rats and found to be effective against *S. aureus* and *Streptococcus pyogenes* (Saporito et al. 2018). Moreover, antimicrobial suspension of triclosan and α-bisabolol encapsulated in chitosan-coated nanocapsule inhibiting a pathogenic strain of *P. aeruginosa* resistant to triclosan became susceptible to a dose nearly eightfold smaller and was thus used commonly in wound dressing (Marchi et al. 2017).

Furthermore, liposomal formulations seemed superior for the treatment of fungal and parasitic diseases compared to their free drug counterpart. In many examples, the toxicity of the antibiotic was dramatically reduced which enable larger amounts of drug targeting to the infected tissues. This increased the efficacy of the treatment by increasing the therapeutic index of liposomal formulation and reducing the side effects. An excellent example to compliment the above statement is the liposomal formulation of amphotericin B, which is the leading drug against leishmaniasis and other fungal infections. The liposome encapsulation reduced its toxicity by 50–70-fold, which allowed more than fivefold administration as compared to conventional treatment. The nanoliposome formulations such as AmBisome® and DepoCyt[e] are today marketed as the most effective treatment for leishmaniasis and other fungal infections which are FDA approved (Sundar and Prajapati 2012). Besides AmBisome®, other formulations of amphotericin B lipid nanostructures were reported to be effective in amoebic meningitis, candidiasis and invasive fungal infections, even in immune-compromised patients (Ringden et al. 1991; Cornely et al. 2007). Nanomicelles of amphotericin B and sodium deoxycholate sulphate when used as aerosol inhalation for lung infection were reported to inhibit *Cryptococcus neoformans* and *Candida albicans* and were also found to significantly improve antileishmanial activity (Usman et al. 2018). Another liposomal formulation under investigation is buparvaquone that has an immunomodulatory effect on the host cells and is highly effective at low doses in eliminating *Leishmania infantum* parasites (da Costa-Silva et al. 2017).

Several other liposomal formulations have also been reported as effective antiviral agents; for example, polyunsaturated endoplasmic reticulum liposomes, commonly known as PERL, target the cholesterol synthesis within infected cells in a large number of viral systems, including hepatitis C virus (HCV), hepatitis B virus (HBV) and HIV (Pollock et al. 2010). The matrix 2 protein ectodomain segments (M2eA) corresponding to the H1N1, H5N1 and H9N2 influenza strains were formulated using a novel liposome-based vaccine technology and were evaluated as potential immunogens which could be used for the development of influenza vaccine (Ernst et al. 2006). At the moment, a number of liposome formulations are in

clinical trials as an adjuvant for prophylactic as well as therapeutic vaccines against malaria, influenza, tuberculosis (TB), human immunodeficiency virus (HIV) and dengue fever, whereas Cervarix®, Inflexal®, Epaxal® and Gardasil® are commercially available liposome vaccines against infection by human papilloma virus (HPV), influenza virus and hepatitis A virus, respectively (Bernasconi et al. 2016). Polymeric nanocapsules consisting of protamine and arginine-rich polymers were recently reported to elicit higher protective immune response as recombinant hepatitis B surface antigen in mice model which may become an alternative antigen delivery vehicle (Peleteiro Olmedo et al. 2018).

5.3.2 Dendrimers

Dendrimers are hyperbranched monodispersed macromolecules with low polydispersity with micelle-like behaviour and nano-reservoir properties (Fig. 5.5a). Dendrimer is a three-dimensional globular structure consisting of a central core, an interior dendritic structure (the branches) and an exterior surface with functional groups, all made up of polymers (Svenson and Tomalia 2012). They differ from classical polymers in two main characteristics: firstly, they are never synthesized by polymerization reactions, instead a step-by-step process, affording to a perfectly defined and highly reproducible structure, and secondly, they have a highly branched

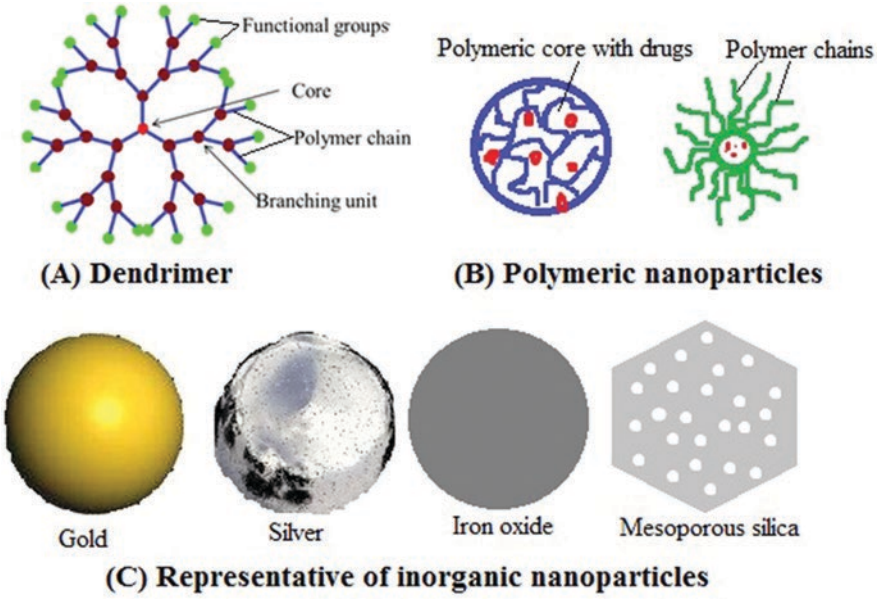

Fig. 5.5 Structures of (**a**) dendrimer with a core and polymer chain, (**b**) polymeric nanoparticles with hydrophilic and hydrophobic core and (**c**) inorganic nanoparticles

3D architecture due to the use of at least one type of branching units as building blocks for their synthesis. Their peculiar structure, reasonable cost of manufacture, toxicological profile and biocompatibility distinguished them from other nanosized species used for polyvalent or multivalent drug discovery/delivery.

Most commonly used polymers for the synthesis of dendrimers are polyamidoamine (PAMAM) and polypropylene imine (PPI). Both PAMAN- and PPI-derived dendrimers have been reported to possess therapeutic value in treating viral and bacterial diseases as well as inflammation (Gong et al. 2002; Chauhan and Jain, 2003). Though dendrimers are known to possess therapeutic properties, they are highly toxic. In order to reduce their cytotoxicity, they are often modified with PEG, carbohydrates, hydroxyl or carboxyl groups to improve their surface activities, as well as their biological and physical properties (Gajbhiye et al. 2007; Ziemba et al. 2011; Kolhatkar et al. 2007).

The antimicrobial potential of dendrimers depends largely upon the type and size of the attached functional groups. Smaller dendrimers are effective, as bulkier dendrimers are unable to pass through the cell membrane and have difficulty in reaching the target site for the anticipated antimicrobial action (Sadegh-Hassani and Nafchi 2014). Amino-terminated PAMAM was found to possess strong antibacterial activity as compared to hydroxyl-PAMAM and carboxyl-PAMAM. This is because the protonated amino group on PAMAM promotes the disruption of the bacterial membrane through electrostatic interaction (Xue et al. 2015). Thus, antimicrobial activity of dendrimers is mostly due to their cationic interaction with the negatively charged bacterial cells. These interactions increase internalization of dendrimers and destroy the membrane proteins which disturb the potassium ion distribution around the bacterial cells. The disturbance caused by the dendrimers completely disintegrates the bacterial membrane causing a bactericidal effect (Chen and Cooper 2002; Cheng et al. 2007). Biocompatible phloroglucinol succinic acid dendrimers were reported to possess an inhibitory effect against a number of gram-positive and gram-negative bacteria (Kumar et al. 2015). Another class of amine- and ammonium-terminated carbosilane cationic dendrimers has demonstrated antimicrobial activity against both gram-positive and gram-negative bacteria (Ortega et al. 2008). Carbosilane dendrimers and dendrons functionalized with guanidine were found to be microbicidal against *E. coli*, *Staphylococcus aureus* and methicillin-resistant *S. aureus* bacteria and against *Acanthamoeba polyphaga* (Heredero-Bermejo et al. 2018). Additionally, hyperbranched PAMAM functionalized with N-diazeniumdiolate nitric oxide, a nitrous oxide (NO) donor, proved effective against common dental pathogens (Yang et al. 2018). Moreover, the conjugated polyglycerols with O-carboxymethylated chitosan and boron suppressed the proliferation of *S. aureus* and *Pseudomonas aeruginosa* (de Queiroz et al. 2006). Additionally, the poly(quaternary ammonium) polymers were engineered for antibacterial specificity and their ability to delay the development of bacterial resistance. These linear poly(quaternary ammonium) homopolymers and block copolymers showed structure-dependent antibacterial specificity toward gram-positive and gram-negative bacterial species by mimicking the behaviour of surface-presented polycationic biocides (Ji et al. 2017).

As an antifungal agent, PPI was shown to improve the solubility of clotrimazole and enhance its antifungal activity against species of *Candida* (Winnicka et al. 2011). Dendrimeric lipopeptides were reported to cause morphological changes in fungal cells and inhibit the enzyme activity of 1,3-β-d-glucan synthase in *Candida* (Janiszewska et al. 2012). The development of dendrimeric peptides (multiple strand protein conjugates) with lysine core was also found to be potent against a number of bacterial species (Tam et al. 2002; Scorciapino et al. 2012) and efficiently kill gram-negative bacteria including the two of the most problematic multidrug-resistant bacteria worldwide *P. aeruginosa* and *Acinetobacter baumannii* (Siriwardena et al. 2017). The central role of peptides in eliciting immune response and development of vaccines against infectious diseases including viral diseases are emerging which can be the most cost-effective methods of improving public health. Induction of immune responses by DNA vaccines formulated with dendrimer and poly-methyl methacrylate (PMMA) was strong and effective in inducing specific antibody and cellular responses thereby reducing the parasite *Leishmania* in mice model (Tabatabaie et al. 2018). Additionally, the DNA vaccines based upon PAMAM-lysine elicited a predominant antibody response with an increase in the production of interleukins (IL-2) to provide protection against *Schistosomiasis japonica* infection (Wang et al. 2014).

5.3.3 Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are one of the most studied organic nanostructures for application in nanomedicine because it is prepared from either natural or semi-synthetic polymers. Due to their synthetic precursors, they can entrap drug molecules in its lipid core or may be covalently bonded to the drugs (Fig. 5.5b). These PNPs are stable, biodegradable and biocompatible and can be easily distributed in the living system due to their building block similarity with biological components. The drug or bioactive molecules in PNP are either dissolved or entrapped or encapsulated or attached to a nanoparticle matrix which can thus improve the diagnosis and treatment of a wide range of diseases, ranging from cancer, viral infections and cardiovascular diseases to pulmonary and urinary tract infections (Hajipour et al. 2012). In the polymeric antimicrobial drug delivery systems, drug molecules can be incorporated in the core of the particles or covalently or non-covalently bonded on the surface of polymeric nanocarriers or encapsulated in the PNPs (Michalak et al. 2016).

Another group of PNPs include nanohydrogels which are extraordinary nanostructures that have the capability to hold a large quantity of water within them. These substances with high water content are synthesized from cross-linked polymers that also have the ability to deliver various drugs or a variety of therapeutic agents in the living system. The first well-known hydrogel developed for biomedical applications was polyhydroxyethyl methacrylate that enabled self-regulated drug delivery systems (Lee et al. 2013). The polymer-based nanoparticles' applica-

tions include drug delivery, wound healing (Greenhalgh and Turos 2009) and antimicrobial activity (Torus et al. 2007). These nanostructures being synthesized using non-biodegradable polymers, such as poly(methyl methacrylate) (PMMA), polyacrylamide, polystyrene and polyacrylates (Torus et al. 2007; Bettencourt and Almeida 2012; Vijayan et al. 2013) suffer from their disadvantageous traits such as chronic toxicity and inflammatory reactions, leading to a shift towards biodegradable polymers. Biodegradable polymers include synthetic polymers such as poly(lactide) (PLA), poly(lactide-co-glycolide) copolymers (PLGA), poly(ε-caprolactone) (PCL) and poly(amino acids) in addition to natural polymers such as chitosan, alginate, gelatin and albumin (Elsabahy and Wooley 2012; Zhang et al. 2013).

Generally, PNPs may interact with the bacterial cell wall either via passive or active targeting. Passive targeting is based on particle size and the ability of particles to disturb the cell wall of bacterial membrane and damaging it. For active targeting of PNPs, the surface of polymeric nanoparticles is usually functionalized with specific antibodies and aptamer bacteriophage proteins that provide specific identification of the pathogens and interaction between the particles and pathogens. The reported studies revealed that both the active and passive targeting strategies to deliver antimicrobial agents with PNPs improve their activities compared to their free form (Kavruk et al. 2015; Barreras et al. 2016). To date, a significant number of reports on the activity of antibiotic-conjugated polymeric nanoparticles against various infections, including those caused by drug-resistant pathogens, have been published. The most common is chitosan nanoparticle either alone or loaded with different metal ions such as copper, manganese, zinc, iron and silver that caused an inhibitory effect in numerous gram-positive and gram-negative bacteria including multidrug-resistant strains (Qi et al. 2004; Du et al. 2009; de Paz et al. 2011; Cremar et al. 2018). The cationic chitosan nanoparticles interact with the anionic surfaces of the microbial cell membrane thereby hindering microbial activity. Chitosan nanoparticle being a biocompatible antioxidant possesses an inhibitory effect against *Candida albicans* (Mubarak Ali et al. 2018) and *Fusarium oxysporum* (Dananjaya et al. 2017). However, in pulmonary infection associated with *P. aeruginosa*, tobramycin alginate/chitosan nanoparticles demonstrated DNA degradation and improved nanoparticle penetration (Deacon et al. 2015). A similar effect was reported using nanohydrogels, for example, ZnO nanoparticles incorporated in nanohydrogel particles made out of sodium alginate/gum acacia and cross-linker glutaraldehyde ensured their gradual and sustained release and demonstrated desired level of antibiotic activity against *P. aeruginosa* (Chopra et al. 2015). Moreover, delivery of levofloxacin, a fluoroquinolone antibiotic scarcely efficient in intracellular infections, entrapped within polysaccharide nanohydrogels efficiently increased the antibacterial activity of the formulation against *P. aeruginosa* and *S. aureus* (Montanari et al. 2014). However, biocompatible PNPs composed of chitosan/sodium tripolyphosphate (TPP) and encapsulated with mercaptosuccinic acid (MSA) acted as spontaneous nitric oxide (NO) donors, with free NO release showing a significant decrease in the percentage of macrophage infected with amastigotes of *Trypanosoma cruzi* (Seabra et al. 2015).

Furthermore, antibacterial property of PMMA containing silver nanofibre was reported against *E. coli* and *S. aureus*, where release of biocidal Ag^+ ions from polymer matrix embedded with silver bromide nanoparticles was able to kill both airborne and waterborne bacteria and also resisted the formation of biofilms (Kong and Jang 2008; Sambhy et al. 2006). Furthermore, drug-loaded PNPs offer added advantages with the ability of stimuli-responsive release of drugs, for example, levofloxacin-loaded PNPs and ciprofloxacin-loaded PNPs against biofilm cells of *E. coli* (Cheow et al. 2010; Singh et al. 2018). Another drug-encapsulated, pH-responsive, surface charge-switching poly(d,l-lactic-co-glycolic acid)-b-poly(l-histidine)-b-poly(ethylene glycol) nanoparticles were able to potentially treat gram-positive, gram-negative and polymicrobial infections associated with acidity (Radovic-Moreno et al. 2012). Similarly, nystatin-loaded PLGA and PLGA-glucosamine nanoparticles exhibited higher antifungal activity (Mohammadi et al. 2017).

5.3.4 Inorganic Nanoparticles

Inorganic nanoparticles, including gold, silver and oxides of iron, titanium, zinc or silicon, and ceramic nanoparticles such as silica and alumina are continuously being investigated in both preclinical and clinical studies for the treatment, diagnosis and detection of many diseases (McCarthy and Weissleder 2008; Na et al. 2009; Giljohann et al. 2010; Huang et al. 2011; Li et al. 2012). Many inorganic metals such as platinum (e.g. cisplatin, carboplatin, oxaliplatin), gold, silver and copper had been in clinical use for centuries, but the understanding of their antimicrobial effect is only a few decades old due to recent studies in their nanoscale dimensions (Zhang and Lippard 2003; Harper et al. 2010). The significant changes in the property of materials that exist in their nanoscale dimension compared to their bulk counterparts are the only reason for their exploration in the field of nanomedicine. It is established that as the size of the material decreases, the proportion of surface atoms increases, thereby increasing the reactivity of these surface atoms (Hanemann and Szabó, 2010). Inorganic nanoparticles are currently explored for their potential use both as therapeutics and drug delivery agents because of the advantage of chemical and mechanical stability as well as surface functionalization with tunable particle size and morphology. Another reason for which inorganic nanoparticles have emerged as potential antimicrobial agents is their relatively low cost, low toxicity and biocompatibility (Huh and Kwon 2011). Silver nanoparticles are known to possess antibacterial and antiviral properties that even acts against HIV and hepatitis viruses (Galdiero et al. 2011). Similar is the case with multivalent gold nanoparticles (Bowman et al. 2008). Recently, nanostructured oxides consisting of two or more metallic components forming core-shell architecture such as Ag-SiO2, Fe3O4/TiO2 and Ag/Fe3O4 demonstrated promising results due to their unique physiochemical properties (Cioffi et al. 2005; Chen et al. 2008; Banerjee et al. 2011). The monometallic gold and silver and bimetallic gold-silver nanoparticles with biologi-

cal activity against five opportunistic *Candida* strains demonstrated high antifungal activity against *C. parapsilosis*, *C. krusei*, *C. glabrata*, *C. guilliermondii* and *C. albicans* (Gutiérrez et al. 2018). In malaria, metal-chelating agents seem to be promising therapeutic adjuvants for treatment against severe *Plasmodium falciparum* infection, and ferroquine, an iron-chloroquine derivative, has been found active against both chloroquine-susceptible and chloroquine-resistant *P. falciparum* and *P. vivax* strains (Sekhon and Bimal 2012).

In general, the inorganic nanoparticles may be engineered to evade the pathogenic system by varying their size and composition (Fig. 5.5c). They may be porous and act as a reservoir to physically encage and protect an entrapped molecular payload from degradation or denaturisation, or may allow surface interaction to hold the drug molecule just as ligand binding (Roy et al. 2003). Like their organic therapeutic counterparts, inorganic therapeutics can benefit from being formulated as a nanoparticle delivery system to improve their biological performance by enhancing pathological targeting, drug loading and immune system evasion (Farokhzad and Langer 2009; Peer et al. 2007). Certain inorganic nanoparticles can respond to specific external stimuli such as magnetic fields or near-infrared light to facilitate on-demand drug release (Timko et al. 2014). The advantage of using these inorganic nanomaterials as antimicrobial agents is that they contain mineral elements essential to humans and exhibit strong activity even when administered in small amounts. Inorganic nanoparticles are particularly interesting because they can be prepared with tuneable morphology. It has already been established that the antibacterial activity of inorganic nanostructures is directly influenced by different structural morphologies (Zhang et al. 2007; Talebian et al. 2013).

Several metal (Au and Ag) and metal oxide (ZnO, CuO, NiO, Sb_2O_3, MgO, Gd_2O_3, SnO_2, WO_3, ZrO_2, Fe_2O_3, TiO_2, CeO_2, Al_2O_3, Bi_2O_3, etc.) nanoparticles have been shown to inhibit the growth of different gram-positive and gram-negative bacteria by changing the membrane permeability, altering metabolic pathways, affecting DNA replication followed by altering transcription and translation processes and most importantly by increasing the intracellular level of metal ions (Applerot et al. 2012; Zhou et al. 2012, Horie et al. 2012). Though the exact mechanism of antimicrobial activity caused by these metallic nanoparticles is not completely understood, there are strong evidences that the inhibition is caused by the generation of reactive oxygen species (like hydroxyl radicals or superoxide anions or hydrogen peroxide), or oxidative stress or free metal ion toxicity arising from the dissolution of metals from the surface of the nanoparticles or the combination of one or more processes that disrupts the normal metabolic activities of the organism thereby killing them. Furthermore, morphological and physicochemical characteristics of the nanometals have been proven to exert an effect on their antimicrobial activities. The positive surface charge of the metal nanoparticles facilitates their binding to the negatively charged surface of the bacteria which may result in an enhancement of the antimicrobial activity (Dutta et al. 2012; Dizaj et al. 2014; Tee et al. 2016; Raghunath and Perumal, 2017). The mechanism of antimicrobial action of metals and metal oxides is schematically represented in Fig. 5.6.

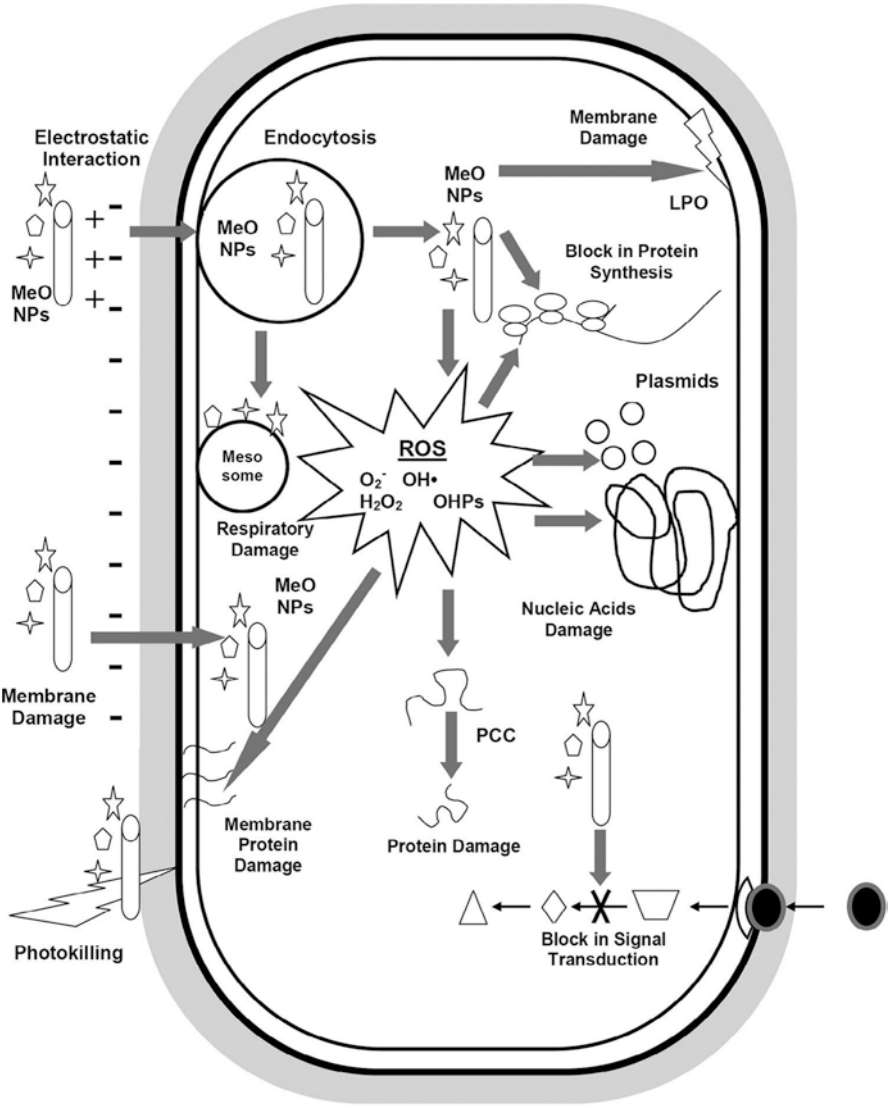

Fig. 5.6 An overview of the antimicrobial mechanism of inorganic nanoparticles. (Printed with permission from Raghunath and Perumal 2017)

Additionally, in the quest to fight AMR, inorganic nanomaterials have emerged as promising candidates since they possess greater durability, lower toxicity, higher stability and selectivity and above all their inhibitory effect against a wide range of multidrug-resistant strains (Pelgrift and Friedman, 2013). Moreover, the antifungal activity of gold, silver and zinc oxide nanoparticles was hugely effective in controlling the growth of *Aspergillus*, *Candida*, etc. (Nasrollahi et al. 2011; Wani and

Ahmad, 2013; Kairyte et al. 2013). In the fight against parasitic diseases such as malaria, leishmaniosis, schistosomiasis and toxoplasmosis, nanoparticles of silver, gold, titanium oxide, alumina, selenium and zinc oxide were able to control the proliferation and binding of the parasite to the host (Allahverdiyev et al. 2011a, 2011b; Soflaei et al. 2014; Marimuthu et al. 2011; Nadhman et al. 2014, Gogoi, 2017).

5.3.5 Carbon Nanostructures

Carbon nanostructures consist of many forms of nanocarbon that can be divided into three groups depending on their dimensions: (i) zero-dimensional (0D) such as fullerene, carbon dots, and nanodiamonds; (ii) one-dimensional (1D) such as carbon nanotubes (CNT), including single and multiwalled CNTs; and (iii) two-dimensional (2D) such as graphene and layered graphene sheets or nanoribbons (Aguilar, 2012). These carbon nanostructures find application in different emerging areas due to their unique properties and are known to exhibit significant antimicrobial properties (Dizaj et al. 2014).

Fullerenes are spherical cage-like nanostructures made exclusively of carbon atoms (e.g. C60, C70). Their unique hollow shape and structural analogy with cellular vesicles make it an excellent drug delivery agent (Tripathi et al. 2015). Fullerenes display diverse biological activity, which arises from the fact that it can act either as an electron acceptor or donor. Fullerenes when irradiated with ultraviolet or visible light can convert molecular oxygen present within the cells into highly reactive singlet oxygen that can damage cellular membranes, inhibit the activity of various enzymes or may even lead to DNA cleavage. The photodynamic therapy (PDT) induced by fullerenes conjugated with photosensitizers had been exploited to control the growth of a broad spectrum of bacteria and fungi (Huang et al. 2010). For example, the cationic-substituted fullerene derivative when illuminated with white light effectively killed gram-positive (*S. aureus*), gram-negative bacteria (*E. coli*) and fungus (*C. albicans*) (Mizuno et al. 2011). A similar effect was reported with fullerenes bearing cationic charges from the addition of potassium iodide and irradiated with ultraviolet A (UVA) or white light killing *A. baumannii*, methicillin-resistant *S. aureus* and fungal yeast *C. albicans* in infected mouse (Zhang et al. 2015). The fullerene-mediated PDT of mice infected with *P. mirabilis* revealed 82% survival compared to 8% survival without treatment, whereas mice infected with highly virulent *P. aeruginosa* survived up to 60% when PDT was combined with an antibiotic, tobramycin (Lu et al. 2010). It has also been found that fullerene PDT is effective in healing wounds infected with pathogenic gram-negative bacteria (Sharma et al. 2011). Functionalized fullerenes with polycationic conjugates and stable synthetic bacteriochlorins allowed PDT to treat infections in animal models (Hamblin 2016). Additionally, biocompatible composites containing polysaccharides (cellulose, chitosan and γ-cyclodextrin) and fullerene derivatives substantially increased the composite's ability to reduce the growth of antibiotic-resistant bacteria such as vancomycin-resistant *Enterococcus* (Duri et al. 2017) (Fig. 5.7).

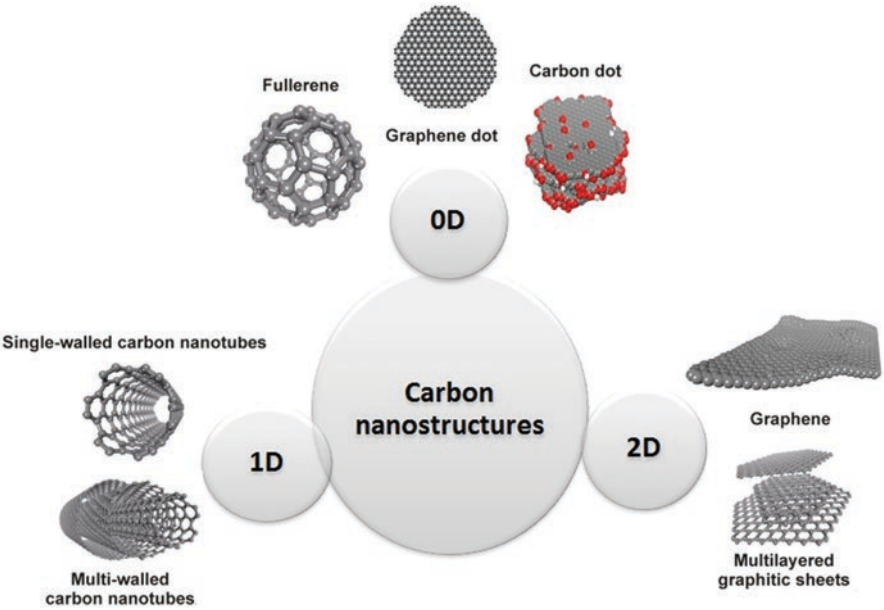

Fig. 5.7 Carbon nanostructures based on their dimensions

Carbon nanotubes (CNTs) are nanosized hollow cylindrical form of carbon formed by a single cylindrically shaped graphene sheet (single-walled carbon nanotubes, referred usually to as SWCNT) or several graphene sheets arranged concentrically (multiwalled carbon nanotubes, referred to as MWCNT). The antimicrobial activity of SWCNTs is attributed to severe membrane damage that leads to cell death. Studies revealed that SWCNTs proved to be potent bactericidal against gram-positive and gram-negative bacteria than MWCNTs because SWCNTs could penetrate into the cell wall better than MWCNTs due to their smaller diameter which initiated better interaction with the cell surface (Kang et al. 2007; Yang et al. 2010; Dong et al. 2012). CNTs coated with silver exhibited antimicrobial activity against mucoid and nonmucoid strains of *P. aeruginosa*. The mechanism of bactericidal effect was attributed to cell membrane integrity, downregulation of virulence-gene expression and induction of oxidative stress (Dosunmu et al. 2015). Additionally, improved bactericidal activity of PEGylated silver-coated SWCNT than their non-PEGylated counterparts was reported against *Salmonella enterica* serovar *Typhimurium* (Park et al. 2018). However, MWCNTs coated with silver and iron nanoparticles proved to be effective antimicrobial in water treatment (Ali et al. 2017) and the composites of lignin MWCNTs with polyvinyl alcohol for applications in wound dressings, scaffolds and antimicrobial textiles (Lee et al. 2018).

Compared with fullerenes and CNTs, graphene (an atom-thick sheet of graphite) and graphene oxide (an oxidized form of graphene) nanosheets present extraordi-

nary physicochemical properties which are responsible for their antimicrobial activities. The inhibitory effect of graphene on bacteria *E. coli, S. aureus* and *P. aeruginosa* and fungi *C. albicans*, *Aspergillus niger* and *A. flavus* has been reported in several studies (Palmeiri et al. 2018; Nguyen et al. 2019). Moreover, the photothermal effect of graphene oxide (GO) as antibacterial (against *S. aureus, P. aeruginosa*), antifungal (against *Saccharomyces cerevisiae* and *Candida utilis*) and in controlling the wound infection using near-infrared laser was also investigated and demonstrated promising result (Khan et al. 2015). Though the antimicrobial efficacy of graphene and GO is impressive, it is found to be toxic to mammalian cells. In order to reduce toxicity and increase the efficiency of GO, surface modification and functionalization with inorganic nanostructures, biomolecules and polymers are done and found to be effective against multidrug-resistant bacteria (Yousefi et al. 2017). The synergistic effect of nanomaterials such as metals, metal oxides and polymers with graphene-based nanostructures for stability and biocompatibility has a wide range of applications in antibacterial packaging, wound dressing and water disinfection (Ji et al. 2016). GO nanocomposites with metallic nanoparticles such as Ag, Au, Cu, Mg and Fe exhibit improved antibacterial as well as antifungal activity as compared to GO due to lower cytotoxicity (Li et al. 2013; Cui et al. 2014; Ji et al. 2016). Graphene nanocomposites containing poly-N-vinyl carbazole (PVK) showed higher bacterial toxicity against gram-negative bacteria *E. coli* and *Cupriavidus metallidurans* and gram-positive bacteria *B. subtilis* and *Rhodococcus opacus.* The nanocomposite encapsulated the bacterial cells, which led to reduced microbial metabolic activity and cell death (Carpio et al. 2012). Graphene-based nanomaterials functionalized with metal nanoparticles, photocatalysts, polymers and biocidal compounds were tailored for antimicrobial activities, used for water disinfection and for the development of antimicrobial polymeric membranes (Zhu et al. 2017). A potent bacterial effect was also reported when metal oxide nanoparticles were grown on the surface of chitosan-modified GO (Chowdhuri et al. 2015) and with chitosan-iron oxide-coated GO nanocomposite hydrogel (Konwar et al. 2016). Recently, the antiviral effect of silver nanoparticle-modified GO nanocomposites against porcine epidemic diarrhoea virus (PEDV) prevented the entry of the virus into the host cells and enhanced the production of interferon-α (IFN-α) and IFN-stimulating genes (ISGs), which directly inhibit the proliferation of the virus (Du et al. 2018).

Though a thorough understanding of the antimicrobial mechanism of graphene-based nanomaterials is still in its infancy, the physicochemical interaction between graphene and microbes is proposed to fall under any of the three categories, namely, (a) nano-knives derived from the action of sharp edges, (b) oxidative stress-mediated with/without the production of reactive oxygen species and (c) wrapping or trapping bacterial membranes derived from the flexible thin-film structure of graphenes (Zou et al. 2016).

5.3.6 *Quantum Dots*

Quantum dots (QDs) are semiconductor nanostructure with diameters in the range of 2–10 nm. These nanostructures emit light of varied colours depending on their size and shape. Due to their glowing properties, QDs are commonly used in imaging, sensors and biology (Frecker et al. 2016). A good number of researches have also established QDs as antimicrobial agents. These include QDs of inorganic heavy metal origin such as cadmium tellurium (CdTe), cadmium selenide (CdSe), cadmium sulphide (CdS), zinc oxide (ZnO) and carbon dots (C-dots) and their functionalized derivatives. Antibacterial activity of CdTe, CdSe and CdS QDs against *E. coli* was reported in a number of studies (Lu et al. 2008; Li et al. 2009). These QDs were investigated to understand its antimicrobial property; experiments indicated that the QDs bind with bacteria and impair the functions of cell's oxidative system via reactive oxygen species (ROS)-mediated pathway and Cd^{2+} ion release. The ROS and released Cd^{2+} ions lead to downregulations of antioxidative genes, and decreases of antioxidative enzyme activities, oxidative damage of protein and lipid and glutathione depletion were responsible for the QDs' cytotoxicity (Lu et al. 2008; Li et al. 2009). Besides, CdTe, CdSe and CdS and ZnO QDs proved to be effective against *Listeria monocytogenes*, *Salmonella enteritidis* and *E. coli* when bound in polystyrene film or suspended in polyvinylpyrrolidone gel (Jin et al. 2009). Quantum-sized silver nanoparticles stabilized with polyvinylpyrrolidone (PVP) inhibited the growth of *C. albicans* that was resistant to conventional antifungal drugs (Selvaraj et al. 2014). Similarly, the germicidal effect of different QDs coated with indolicidin was observed against *S. aureus*, *P. aeruginosa*, *E. coli*, and *Klebsiella pneumonia* (Galdiero et al. 2016). Furthermore, the nanocomposites of QDs such as chitin-CdTe films and CdSe QD-ZnO exhibited excellent antibacterial activity against gram-positive and gram-negative bacteria (Wansapura et al. 2017; Mahmoodi et al. 2018). Research showed that conjugation of QDs with different nanomaterials enhanced their antimicrobial activity; for example, the germicidal action of MWCNTs was reported to be poor against different bacterial strains, but when MWCNTs were conjugated with CdS and Ag_2S QDs, its antimicrobial activity improved severalfold (Neelgund et al. 2012). Similarly, gold-carbon dot (Au-C-dot) nanoconjugate exhibited a profound effect on the susceptibility of a fungus, *C. albicans* (Priyadarshini et al. 2018).

C-dots, graphene and graphene oxide QDs (GOQDs) are known to be "safe" carbon nanomaterials and an effective antimicrobial agent. Their mechanism of microbial cell death is linked to the peroxidase-like activity that catalyzes the decomposition of H_2O_2, generating free radical, •OH. Since the •OH has higher antibacterial activity, the conversion of H_2O_2 into •OH improves the antibacterial performance. This property of graphene QDs is effective against both gram-negative (*E. coli*) and gram-positive (*S. aureus*) bacteria and in wound healing (Sun et al. 2014). The photoexcitation of graphene QDs (GQDs) leads to the generation of ROS which is found to inhibit *E. coli* and methicillin-resistant *S. aureus* (Ristic et al. 2014). GQDs doped with nitrogen and functionalized with an amino group

serving as a photosensitizer in photodynamic therapy had superior ability to generate ROS as compared to unmodified GQDs, which were able to completely eliminate multidrug-resistant species (Kuo et al. 2018). Similarly, sulphur- and nitrogen-doped C-dots demonstrated improved antibacterial activity against gram-negative, gram-positive and drug-resistant bacterial strains (Travlou et al. 2018). Moreover, antibiotic attached to C-dots proved to be an effective nanocarrier for controlled drug release and high antimicrobial activity against both gram-positive and gram-negative bacteria (Thakur et al. 2014). Similar antibacterial activity was observed against *P. aeruginosa* when C-dots were doped with gallium (Kumar et al. 2017). Antiviral activity of C-dots was achieved with surface functionalization with 2,2′-(ethylenedioxy)bis(ethylamine) (EDA) and 3-ethoxypropylamine (EPA). Both EDA and EPA C-dots effectively inhibited the binding of two strains of human norovirus-like particles (VLPs) to histo-blood group antigen (HBGA) receptors on human cells (Dong et al. 2017).

5.3.7 Electrospun Nanofibres

Polymer fibre materials that are shrunk from micrometre to submicron or nanometre scale show amazing characteristics such as large surface area to volume ratio, flexibility in surface functionalities and higher mechanical performance (stiffness and tensile strength). These superior properties make the polymer nanofibres (NF) optimal candidates for many applications such as filtration membranes, catalytic nanofibres, fibre-based sensors and tissue engineering scaffolds (Jayakumar et al. 2010; Ma and Hsiao 2018; Haider et al. 2018). In order to synthesize these nanofibres, several processing techniques such as drawing, template synthesis, phase separation, self-assembly and electrospinning have been used (Huang et al. 2003). Among these techniques, electrospinning has gained popularity recently due to the production of polymer fibres with diameters varying from 3 nm to 5 μm. Electrospinning provides multiple desirable features for wound dressings, including high absorptivity due to high surface-area-to-volume ratio, high gas permeation and conformability to a contour of the wound bed (Lalani and Lui 2012). The attractive feature of electrospinning is the simplicity and inexpensive nature of the setup; the typical electrospinning setup consists of a syringe pump, a high-voltage source and a collector. The working principle of electrospinning was nicely reviewed by Pham et al. (2006). This approach has been used successfully to spin a number of synthetic and natural polymers such as cellulose, poly(acrylonitrile), poly(caprolactone), poly(methyl methacrylate), poly(vinyl alcohol) and polyimide fibres into nanofibres applied in the fields of biomedicine (wound healing) and biotechnology (Haider et al. 2018).

The electrospun polymeric nanofibres loaded with silver (Ag) nanoparticles, chitosan and their composites have demonstrated excellent antimicrobial activity against bacteria, fungi and parasitic diseases. Electrospun antimicrobial polyurethane nanofibres containing Ag indicated high bactericidal effect against *E. coli* and

S. typhimurium (Sheikh et al. 2009). Nanofibre mats loaded with Ag nanoparticles (~25-nm diameter) enveloped in chitosan and cross-linked with glutaraldehyde showed superior properties and synergistic antibacterial effects (Abdelgawad, et al. 2014). The electrospun cellulose acetate containing Ag nanoparticles on their surface when irradiated with UV exhibited strong antimicrobial activity (Son et al. 2006). Similarly, the electrospun cellulose nanofibre mats decorated with silver ion inactivated *E. coli* (Reiger et al. 2016). Antimicrobial nanofibrous membranes developed from electrospun polyacrylonitrile nanofibres with diameters of ~450 nm loaded with Ag nanoparticles demonstrated a convenient and cost-effective approach to develop antimicrobial nanofibrous membranes that would be particularly suitable for the filtration of water and/or air (Zhang et al. 2011). Additionally, the chitosan-based nanofibres such as a mixture of poly(lactide-co-glycolide) (PLGA) and chitosan when electrospun yielded cylindrical and narrow-diameter (356 nm) polymeric fibres. The PLGA-chitosan mats were then functionalized with graphene oxide and decorated with silver nanoparticles, effectively inactivating both gram-negative (*E. coli* and *P. aeruginosa*) and gram-positive (*S. aureus*) bacteria (De Faria et al. 2015). Chitosan nanofibres electrospunned with poly(ethylene oxide) and silver nitrate, as a co-electrospinning polymer and silver nanoparticle precursor, revealed antibacterial activity (Annur et al. 2015), Similarly, the electrospun fibrous membrane of zwitterionic poly(sulfobetaine methacrylate) (PSBMA) known for its superhydrophilic and ultralow biofouling properties makes it a promising material for superabsorbent and non-adherent wound dressings. Bacterial adhesion studies using gram-negative *P. aeruginosa* and gram-positive *S. epidermidis* showed that the PSBMA electrospun membrane was highly resistant to bacterial adhesion. Moreover, the Ag-impregnated electrospun PSBMA membrane proved microbicidal against both *S. epidermidis* and *P. aeruginosa* (Lalani and Lui 2012). Furthermore, the antimicrobial peptide pleurocidin is known for broad microbial inhibition and thermal/pH tolerance when incorporated with poly(vinyl alcohol) electrospun nanofibre showing higher inhibition efficiency than free pleurocidin against *E. coli* (Wang et al. 2015).

However, for fungal infections, clotrimazole-loaded microemulsion (a mixture of polyvinyl alcohol and chitosan) containing nanofibre mats demonstrated mucoadhesive properties against oral candidiasis and is now developed as an alternative for oral applications (Tonglairoum et al. 2015). Polylactic acid films coated by electrospinning with a formulation containing chitosan demonstrated excellent antifungal activities against *Aspergillus brasiliensis*, *Fusarium graminearum*, *Penicillium corylophilum* (Mitelut et al. 2017). Similarly, electrospun poly(lactic acid) (PLLA) nanofibre membranes loaded with bovine lactoferrin (bLF) membranes display antifungal activity against *A. nidulans* by inhibiting spore germination and mycelial growth (Machado et al. 2018). Moreover, the sustained release of a cellulose acetate solution containing artemisinin, an antimalarial drug, developed from electrospinning of poly(vinyl pyrrolidone) confirmed the higher bioactivity of the released drug from the composite (Shi et al. 2013). Recently, electrospun core/shell nanofibres containing different percentages of artemisinin were developed as new systems for drug administration in malaria. The core consisted of hyperbranched

poly(butylene adipate) and poly(vinylpirrolidone) as shell material, and a controlled proliferation of malarial parasites (*P. falciparum*) was reported in this study (Bonadies et al. 2017)

Though electrospinning is well known for its simplicity and cost-effective setup, its disadvantage lies in the production of fine fibres and low yield (Sarkar et al. 2010). A recently developed method known as Forcespinning® (FS) has shown the capability to produce fine fibres from melt and solution through centrifugal spinning (Padron et al. 2013). The FS method does not require electricity and broadens the choice of materials to be spun into fibres (Padron et al. 2013; Rane et al. 2013). The process is highly controllable at the industrial scale and has shown production rates of up to hundreds of metres per minute. Previous FS studies have successfully produced wound dressings composed of cellulose acetate fibres embedded with silver nanoparticles (AgNPs) and ternary composite fibre dressings such as pullulan/tannic acid/chitosan fibre and polyvinyl alcohol/chitosan/tannic, all of which showed antimicrobial activity (Xu et al. 2015, 2016). Recently, chitosan binary nonwoven fine fibre composite scaffolds composed of chitosan/cinnamaldehyde (CA) and chitosan/AgNPs were produced using FS technology. Cinnamaldehyde and silver are known to possess strong antimicrobial properties and therefore its effect in these binary composites exhibited improved antimicrobial activity against *S. aureus* (Cremar et al. 2018).

5.3.8 Other Potential Nanomaterials Effective Against Microorganisms

Continuous research for the development of new nanomaterials that are potent antimicrobial agent has grown severalfold. Many nanomaterials such as nanodiamonds, nanoribbons, nanopowders and nanoclays have shown their advantages over existing nanomaterials against infectious diseases as well as against multidrug-resistant (MDR) species. For example, the advantage of nanodiamonds (diamond nanoparticles) is that they are completely inert, optically transparent and biocompatible as compared to other carbon-based materials such as fullerenes and carbon nanotubes. Although the *in vivo* toxicity of nanodiamonds (ND) against bacteria and biofilm formation depends on their surface characteristics (Wehling et al. 2014) and functionalization (Turcheniuk et al. 2015), they have been found to be non-cytotoxic to a variety of cell types and have been thus used in a number of biomedical applications (Liu et al. 2007; Marcon et al. 2010; Mochalin et al. 2012). Moreover, functionalized NDs with hydroxyl, amine, carboxyl, saccharides, etc. have found to be an effective antimicrobial and antibiofilm agent (Khannal et al. 2015; Szunerits et al. 2016). The powdered nanoparticles (nanopowder) of Au, Ag, Al_2O_3, Co_3O_4, CuO, Fe_2O_3, Fe_3O_4, MgO, ZnO, NiO SiO_2, graphene, etc. and their doping on hydroxyapatite powders have demonstrated pathogenic effect against bacteria and fungi (Sygnatowicz et al. 2010; Stanić et al. 2010; Marriappan et al. 2017). The

nanopowders were obtained by conventional techniques such as nanoprecipitation, emulsion-diffusion and double emulsification, but recently, with the emergence of electrospraying technique, developing micro- and nanosized particles containing bioactive compounds is booming. Electrospraying improved nanoparticle production such as scalability, reproducibility and encapsulation with biodegradable polymers obtained from food products (proteins, carbohydrates), such as chitosan, alginate, gelatin, agar, starch or gluten (Tapia-Hernandez et al. 2015). Thus, electrosprayed nanoparticles and nanofibres are both employed as natural or synthetic carriers for the delivery of entrapped drugs, growth factors, health supplements and vitamins and as antimicrobial agents (Sridhar et al. 2015; Rodríguez-Tobías, et al. 2016).

Furthermore, nanoclays (nanoparticles of layered mineral silicates) have also been found to be of good importance in polymer nanocomposites and as drug delivery carriers. Depending on the chemical composition and nanoparticle morphology, nanoclays such as commercially available montmorillonite and naturally occurring cloisite have been effective against gram-positive and gram-negative bacteria (Hong and Rhim, 2008). A similar and improved efficiency of cetyltrimethylammonium bromide (CTAB)-modified montmorillonite with poly(butylene adipate-co-terephthalate) nanocomposite films and organo-modified Algerian montmorillonites with poly(ε-caprolactone) was reported to be biodegradable (Mondal et al. 2014; Yahiaoui et al. 2015). The incorporation of biodegradable natural and polymeric materials with nanoclays and their ability to retard microbial spoilage makes them an ideal material for food packaging (Mondal et al. 2014; Jiménez et al. 2016).

5.4 Potential Toxicity of Nanomaterials

Advancement in nanoscience and nanotechnology led to the development of nanomaterials and nanostructures which have been seen as novel alternatives to antibiotics in infectious diseases. However, these nanomaterial-based antimicrobial agents suffer from potential biological toxicity, poor degradation and other secondary pollution. For example, most of the semiconductor QDs made of heavy metal ions (e.g. Cd^{2+}) are responsible for their potential toxicity and their practical applications. Studies on a series of aqueous synthesized QDs, i.e. CdTe, CdTe/CdS core-shell structures and CdTe/CdS/ZnS core-shell-shell structures, revealed cytotoxicity is caused by an increase in the intracellular level of Cd^{2+} ions released from the QDs (Chen et al. 2012). The knowledge on the potential application of some of the metal oxide nanoparticles such as CuO, ZnO, Sb_2O_3, Mn_3O_4 and Co_3O_4 is limited because of their toxicity to mammalian cells at higher concentrations (Gajewicz et al. 2015; Ivask et al. 2015; Hou et al. 2018). It has been proposed that functionalization, ion doping and polymer conjugates of these metal oxide nanoparticles could be helpful to decrease the associated toxicity. Additionally, the toxicity of CNT samples was found to be dependent on its composition along with its geometry and surface functionalization. Several studies have suggested that well-functionalized CNTs are safe

to animal cells, while raw CNTs or CNTs without functionalization show severe toxicity to animal or human cells at even moderate dosage (Khalid et al. 2016). Other nanomaterials such as dendrimers, C-dots and fullerenes have been found to be cytotoxic. According to the reports, neurological and respiratory damage, circulatory problems and some other toxicity effect of nanoparticles are the main concerns with the use of nanoparticles (Elsaesser and Howard 2012; Dijaz et al. 2014). However, several types of nanoparticles such as TiO_2 and ZnO appear to be non-toxic with beneficial health effects; hence, few have been approved by the Food and Drug Administration and are commercially available (Elsaesser and Howard 2012). The cytotoxicity of some nanomaterials demands further research in functionalization and require alternative synthesis processes such that they are harmful to the microbes and not to the mammalian cells. The most common methods for nanoparticle synthesis were chemical and physical that is costly and potentially harmful to the environment. An alternative approach known as "green synthesis" is actively pursued nowadays for an efficient, inexpensive and environmentally safe method for producing nanoparticles with specified properties that are biocompatible and degradable (Marakov et al. 2014; Praveen et al. 2016). The area of green synthesis is rapidly gaining importance due to its growing success and ease of formation of nanoparticles. Presently, the potential of bio-organisms ranges from simple prokaryotic bacterial cells to eukaryotic fungus and even plants.

5.5 Conclusion and Future Prospects

Nanomaterials are showing promising solutions against infectious diseases due to their peculiar size, shape, chemical composition, surface structure, charge, solubility and their interactions with biomolecules and cells. It is well known that biological transport processes, anatomically and down to the cellular and subcellular levels, are affected by the physical attributes of the nanoparticles, including their size, shape and flexibility, as well as their chemical characteristics, including the presence of active ligands for recognition by and triggering of biological receptors. Therefore, it is of critical importance to utilize procedures that prepare nanostructures with high degrees of uniformity and with control over their physical and chemical traits. Though nanomaterials have excellent therapeutic importance, they suffer from the disadvantages of high cytotoxicity, biodegradation or agglomeration which is a major concern. Thus, understanding the nanoparticle and biological interface/interactions though complicated is very essential, especially considering the toxicity fears that currently exist in the field of nanomedicine field. There is a need for a set of design controls to study the nano-biointeractions including studies comprising of both the material properties and biological compositions such as analysis of transport kinetics, clearance, gene expression variations, chemical functionality, surface charge, biomolecular signalling and toxicity. Mostly, inorganic nanoparticles and dendrimers suffer from this problem. Thus, there exist opportunities in tailoring these nanoparticles such that minimum harm is caused to the human cells

without losing their antimicrobial effect. Another area of concern is the stability of the nanomaterials in biological fluids and to withstand the acidic pH of the stomach when administered orally. Liposomes and dendrimers are also susceptible to enzymatic degradation in the gastrointestinal tract. Here the needs of nanocapsules which can withstand the acidic pH are in demand for oral administration. These formulations should be mechanically and sterically stable such that they can survive these conditions and deliver the encapsulated drug via the normal absorption process. Additionally, the passage of therapeutic agents across the blood-brain barrier in neurological infections is a great challenge which can be accomplished by the use of nanomaterials. Nanomaterials can be engineered for treating diseases such as cerebral malaria, meningitis and encephalitis. Recent research in the field of multimetal oxides still demands extensive exploration since the combined effect of two or more particles can be better. Moreover, different nanomaterials are yet to be explored against infections of bacteria, fungi, viruses and parasites, where some may be more effective and safe than the one existing at present. To conclude, it can be stated that the application of nanomaterials against diseases is enormous with innumerable options of synthesizing and tailoring the particles. In view of designing these particles against different diseases, the most important concern must be that it should be safe for its therapeutic application in humans with minimum side effects.

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