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MINIREVIEW

Potential applications of engineered nanoparticles in medicine and biology: an update

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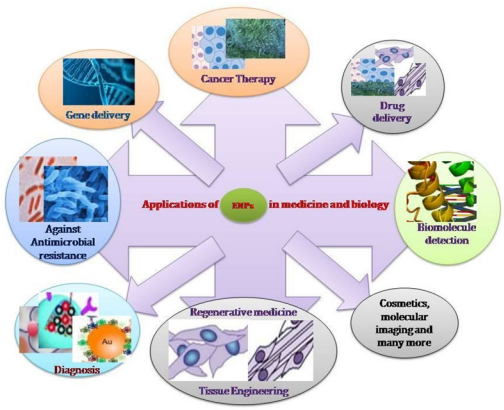
Abstract

Nanotechnology advancements have led to the development of its allied fields, such as nanoparticle synthesis and their applications in the field of biomedicine. Nanotechnology driven innovations have given a hope to the patients as well as physicians in solving the complex medical problems. Nanoparticles with a size ranging from 0.2 to 100 nm are associated with an increased surface to volume ratio. Moreover, the physico-chemical and biological properties of nanoparticles can be modified depending on the applications. Different nanoparticles have been documented with a wide range of applications in various fields of medicine and biology including cancer therapy, drug delivery, tissue engineering, regenerative medicine, biomolecules detection, and also as antimicrobial agents. However, the development of stable and effective nanoparticles requires a profound knowledge on both physico-chemical features of nanomaterials and their intended applications. Further, the health risks associated with the use of engineered nanoparticles needs a serious attention.

Graphical Abstract



Applications of engineered nanoparticles (ENPs) in different fields of medicine and biology.

Keywords Biomedicine · Biomolecule detection · Cancer therapy · Drug delivery · Engineered nanoparticles · Regenerative medicine · Tissue engineering

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Introduction

The multidisciplinary unit, comprising the principles of physics, chemistry, engineering and biology to design and synthesize the nanoscale materials or devices is termed as nanotechnology. Nanotechnology deals with the development of nanoscale sized objects including materials, devices

and/or systems [1]. The rapid progress in nanotechnology has shown a new hope in promoting human and veterinary health and in addressing the deadliest diseases in the future. Currently, it is well accepted with a great concern of potential health risks. The exposure of nanoparticles (NPs) causes inflammation, toxicity, apoptosis, oxidative stress and lung inflammation leading to pulmonary diseases [2, 3]. Further, the presence of ultrafine particles at extra-pulmonary sites including heart, liver, brain, and also in the systemic circulation have been observed to cause intestinal pulmonary fibrosis, metal fume fever, mesothelioma, and ardystil syndrome [3–5]. Nanomaterials typically have a size in the scale of 0.2–100 nm with an increased surface to volume ratio [2]. The NPs are of two different types such as non-engineered NPs which are found in the environment and derived from natural events (erosion, and volcanic eruptions) and engineered NPs (ENPs) produced by human using different materials [6]. The physico-chemical and biological properties of ENPs including strength, flexibility, performance and durability have drawn an attention from various fields such as medicine, biology, and engineering.

The properties of NPs, such as size, shape, surface morphology and particle diameter affect the physical stability and also the performance of NPs in vivo [7]. The surface area of NPs increases with the decreased size and the increased surface to volume ratio is correlated to their increased antimicrobial activity. Different types of ENPs ranging in size from 0.5 to 1000 nm have been synthesized and characterized for their applicability in biomedical fields. Furthermore, the efficiency of ENPs also depends on the surface characteristic features such as surface charge and hydrophobicity. The surface Zeta potential values of NPs helps in the determination of surface charge and surface hydrophobicity [8]. The interaction of NPs with the bioactive compounds depends on the NPs surface charge, intensity and also the electrostatic interaction between them [7]. Depending upon the dimensions, ENPs can be classified as one-dimensional (thin films), two-dimensional (carbon nanotubes) and three-dimensional (dendrimers, quantum Dots) NPs [7, 9]. Many different types of NPs have been developed and characterized for use in drug/bioactive agent delivery system which include liposomes [10], polymeric NPs [11] nanocapsules [12, 13], polymeric micelles [14], and dendrimers [15, 16]. Properties and synthesis of these NPs is discussed in Sect. 2.1. The effectiveness of ENPs in a biological system is mainly correlated to their properties, such as shape, size, configuration, surface charge, and chemical and biological interactions. Application of ENPs in imaging, phototherapy, and drug delivery require a stable and explicit control over NPs interaction with cells, which are mostly provided by the surface properties of NPs [17]. Moreover, the stability and size control issues remains as a challenge during the synthesis of ENPs [18].

The development of advanced techniques, such as transmission electron microscope (TEM) including low- and high-resolution TEM (LRTEM and HRTEM), photon-correlation spectroscopy (PCS), scanning electron microscopy (SEM), atomic force microscopy (AFM), laser doppler anemometry (LDA) have significantly influenced the development of nanomaterials and their characterization. The difference in the surface to volume ratio allows ENPs to exhibit different chemical, physical, electrical, optical, mechanical, and magnetic properties [19, 20]. The physico-chemical and biological properties of ENPs can be modified depending on various applications [1, 21].

NPs possess a specialized property known as stimuli response release system in which the release of bioactive agents can be controlled by various physical and chemical parameters [22, 23]. Different types of stimuli, such as temperature [24], magnetic fields [25, 26], ultrasonic waves [27], pH [28], and light [29] have been investigated as effective stimuli to use in response release systems and this helps in the effective release of bioactive compounds at the target sites. The ENPs are utilized in various fields, such as optical, chemical and biological applications. In specific, they are widely used in the fields of optical devices, superconductors, catalysts, drug delivery, gene delivery, fuel cells, imaging of biosamples, biomolecules detection, tissue engineering, regenerative medicine, detection of pathogens, biosensors and also as alternatives against drug-resistant microbes [2, 30–34].

ENPs exhibit superior inhibitory activity against microbes [35–37]. Both organic as well as inorganic ENPs with potential applications in different fields of life science have been synthesized by several research groups. However, the inorganic ENPs have wide ranging applications when compared to organic ENPs due to their capacity to withstand adverse reaction conditions [21]. Several types of ENPs have been synthesized and characterized by different research groups and are shown in Table 1. Moreover, it has been observed that NPs play a promising role in the delivery of drugs and other bioactive agents with increased therapeutic and/or bioactive efficacy [38, 39]. The role of ENPs in medicine such as in vivo imaging, in vitro diagnostics, tissue engineering, regenerative medicine and also in the detection of biomolecules has been well established [40].

Antimicrobial drug resistance has forced to use alternative approaches for the treatment of various diseases. Amongst them, nanocomposites such as graphene oxide-silver nanocomposites, Ti-GO-Ag nanocomposite, Ag NPs/GO nanocomposites have been reported to be very effective antimicrobial agents [41–43]. The nanocomposites/NPs act on microbes by various ways, including DNA damage, inhibiting DNA replication, protein synthesis, release of reactive oxygen species (ROS) and cell wall/membrane disruption (Table 1). Furthermore, different

Table 1 Different engineered nanoparticles and their mode of antimicrobial actions

Nanoparticles/nanocomposites	Mode of action	References
Aluminum nanoparticles	Disrupt cell walls by generating ROS	[2, 216]
Bismuth nanoparticles	Alter/modify the process of Krebs cycle, nucleotide and amino acid metabolism	[2, 192, 193]
Carbon-based nanoparticles	Cause damages to the bacterial cell membrane, interacts physically and interrupt cell wall, inhibit the respiratory chain	[2, 221, 223]
Copper oxide nanoparticles	Reduce the adhesion of bacterial cell and interrupt the biological processes within the microbial cell	[2, 213–216]
Gold nanoparticles	Disrupt cell wall, attach with DNA and inhibits the DNA replication and transcription	[2, 204, 206, 212]
Iron containing nanoparticles	Generate Reactive Oxygen Species (ROS) because of oxidative stresses which in turn destroy bacterial cell	[2]
Magnesium oxide nanoparticles	Generate ROS, due to electrostatic contact and alkaline effects cells are damaged	[2, 192, 193]
Silver nanoparticles	Affect DNA integrity, prevent DNA duplication process, inhibits electron transport chain and energy transfer	[2]
Titanium dioxide nanoparticles	Release ROS and results in DNA impairment	[2]
Zinc oxide nanoparticles	Generate hydrogen peroxides, Zn^{2+} ions from the nanomaterials cause cell membrane damage	[2, 198, 199, 201]
Ti-GO-Ag nanocomposite	DNA damage, interruption of cell signal transduction, oxidative damage, leak out of intracellular contents, and dehydrogenase inactivation	[41]
Graphene oxide-silver nanocomposites	Oxidative stress,	[42]
AgNPs-graphene oxide (Ag NPs/GO) composites	Synergistic action between graphene oxide and Ag NPs	[43]

types of nanomaterials, such as gold (Au), silver (Ag), silver oxide (Ag_2O), titanium dioxide (TiO_2), zinc oxide (ZnO), copper oxide (CuO), calcium oxide (CaO), magnesium oxide (MgO) and silica (Si) have been synthesized and characterized for their antimicrobial activity [2, 34]. The antimicrobial mechanism of ENPs depends on their bulk properties. NPs which process high surface area to volume ratio reduce the microbial adhesion and the formation of biofilms and are the viable approaches for the treatment of biofilm-associated infections [44]. The development and characterization of magnetic NPs (MNPs) has evolved as a significant field of research in medicine and biology. The growing interest in the MNPs is due to their easy preparation, smaller sizes, higher biocompatibility, low toxicity, high stability, simple chemical functionalization, efficient drug conjugation along with superior magnetic responsiveness [45]. Many different MNPs based on iron oxide have been developed and found potential applications in the field of drug delivery, magnetic resonance imaging, magnetic separation and biomolecules detection and also in the new and emerging fields of medicine, such as cell therapy, tissue engineering, and regenerative medicine.

The present review provides comprehensive and updated information related to various applications of ENPs in medicine and biology. The data in this review has been obtained by various search engines including Science Direct, Google Scholar, Scopus, Pub Med, Research Gate and SciFinder.

Applications of ENPs

Nanotechnology and the development of ENPs have revolutionized the fields of medicine and have given a ray of hope for physicians in combating the diseases which still do not have specific drugs. ENPs find potential applications in various fields of medicine and biology Different types of ENPs have been synthesized and characterized by several groups for this purpose. Some of the inorganic ENPs, such as aluminum NPs (AlNPs), copper NPs (CuNPs), CuONPs, AuNPs, AgNPs, MgONPs and carbon-based NPs have been synthesized, characterized and evaluated for their biological activity. Furthermore, advancements in the field of DNA nanotechnology and preparation of several different DNA-based NPs has been a significant impact in the field of medicine and biology such as drug delivery, and preparation of biosensors/biochips [46]. Various organic ENPs including quaternary ammonium compounds, chitosan, polysiloxanes, and triclosan have also been characterized for their biological activity [2]. Several different metalloid NPs such as polymercoated bismuth sulfide NPs, and cadmium telluride NPs have also been employed in the diagnostic assays [47]. The application of ENPs in various fields is represented schematically in Fig. 1.

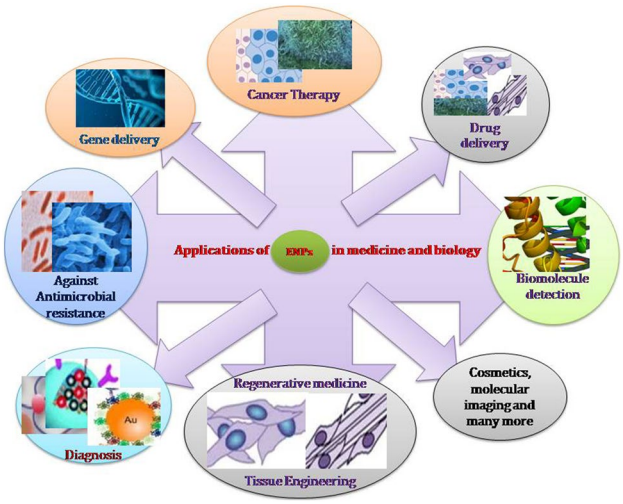

Fig. 1 Applications of engineered nanoparticles in different fields of medicine and biology

ENPs in cancer therapy

The most common and widely used mode of cancer treatments include surgical removal of an abnormal tissue, chemotherapy, biotherapy, radiation therapy alone and/or in combination with two or more different therapies. Though these conventional cancer therapies have improved the patient survivability, they carry certain limitations such as non-specific distribution of drugs, aqueous insolubility of drugs, and multidrug resistance [48, 49]. One of the major shortcoming of conventional therapy is non-specific distribution of drugs, which limits the therapeutic dosage, and also affects the normal cells, tissues and organs with severe side effects, and bring down the quality life of cancer patients [50]. Hence, designing a specific drug to target cancer cells/tissues accompanied by the controlled drug release helps to overcome the shortcomings of conventional cancer therapy and could benefit the cancer treatment significantly.

The development of NPs has offered a great benefit and interest in cancer therapy in addition to overcoming the limitations of conventional chemotherapies [51, 52]. ENPs have several advantages including the enhanced solubility of hydrophobic drugs, prolonged circulation time, capacity to carry higher payloads of drugs, minimized non-specific uptake, prevention of undesirable side effects, enhanced intracellular penetration, specific anticancer drug targeting and in cancer imaging [53, 54]. Drug carriers enter into cancer tissue compartments through openings/fenestrae between vascular endothelial cells and several different NPs can easily pass through these fenestrae [55]. The great advantage of ENPs is their specific drug delivery to target sites such as cancer cells or tumors, which in turn increases the drug concentration at the target site/s by avoiding the toxicity to normal cells. However, the factors such as, molecular weight and stability are attributed to the specific distribution, optimized blood circulation and finally accumulation within tumors. Moreover, the rate of leakage of NPs across tumor vascular fenestrae can also be controlled through several parameters such as shape, size and surface properties, concentration (in tumor blood vessel) of NPs, and blood vessel factors such as the size of fenestrae, density, and distribution [55]. Further, NPs have the great potential in overcoming the multiple drug resistance mechanism in cancer therapy [52]. In addition, ENPs can be tailored to carry therapeutic drugs as well as imaging probes or diagnostic agents simultaneously and also can be designed to target diseased tissues specifically to enable combination therapy to overcome multidrug resistance [56].

Cancer cells display greater affinity towards particles of certain size than healthy cells due to their faulty particle screening and the presence of immature blood vessels which may be leaky and the phenomenon is known as the enhanced permeation and retention (EPR) effect [57, 58]. Hence, the EPR effect allows NPs to accumulate more (100–200 times) into tumor cells/tissue than normal cells/tissues [40] and this mechanism is also considered as a "gold standard" for the designing of anticancer drugs and also for targeting the site of tissue inflammation [40, 59–62]. The approval of cisplatin as an antitumor agent by the Food and Drug Administration (FDA) in 1978 has generated interest in exploring other metals such as gold and gold-based compounds in cancer therapy [63]. The first clinical trial for NPs based anticancer drug delivery started in the mid-1980s, and in 1995, the first liposomal NPs encapsulated with doxorubicin drug had entered the pharmaceutical market. Since then, several new and novel ENPs have been approved or under the development as anticancer drug delivery systems and cancer therapy. Different types of ENPs have been explored in the cancer therapies which include inorganic ENPs, polymeric ENPs and conjugates, micelles, dendrimers, protein and bacterial carriers (Fig. 2). Several different ENPs have been approved as anticancer agents by FDA for metastatic breast cancers, ovarian cancers and Kaposi's sarcomas [64].

Liposome NPs for cancer treatment

Liposomes find potential applications in the cancer treatment due to their unique characteristic features such as biocompatibility, biodegradability, lack of immune system activation, low toxicity, and the capability to encapsulate both hydrophobic and hydrophilic drugs. Thus, liposomes have gained a significant attention as carrier systems for the delivery of therapeutic agents [65]. Moreover, surfaces of liposomes are modifiable through several chemical linkages/strategies to acquire significant therapeutic functions, including site-specific drug delivery, enhanced accumulation at the target site,

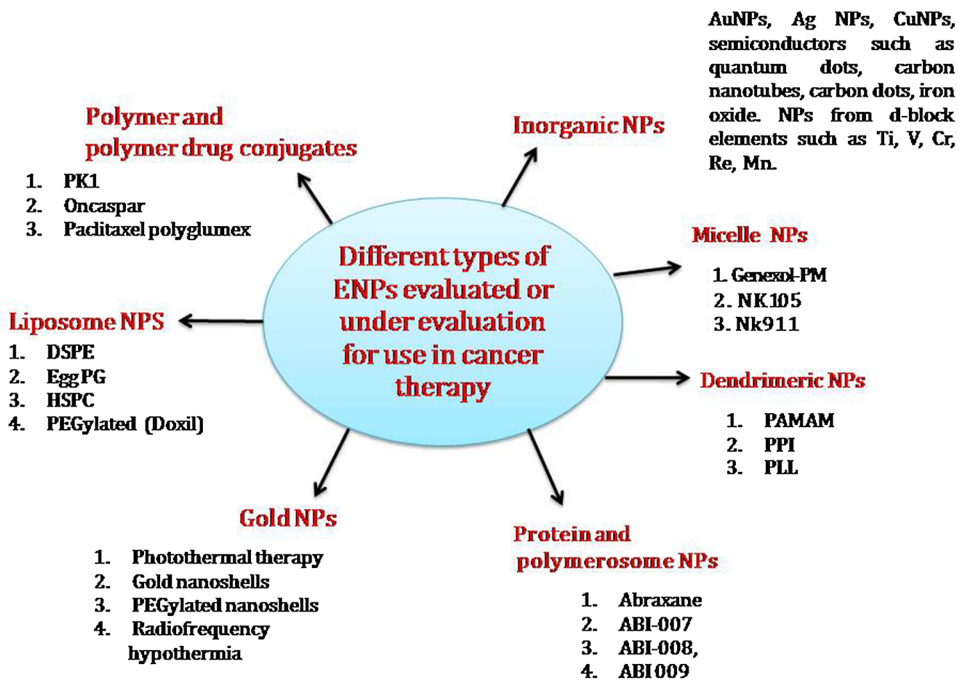

Fig. 2 Different types of engineered nanoparticles (ENPs) approved by FDA or under clinical trial for cancer therapy

prolonged systemic circulation, and increased cellular internalization [66, 67]. The therapeutic potential of liposomes as carriers for payloads and drug delivery to the target sites has led to the development of several different liposomal formulations for cancer therapy [68]. Several such vesicular formulations have been approved by FDA including 1,2-distearoyl-sn- glycero-3-phosphoethanolamine(DSPE), egg yolk phosphatidylglycerol (EggPG), hydrogenated phosphatidylcholine from soybean lecithin (HSPC), and 1,2-distearoyl-glycero-3-phosphocholine (DSPC) [67].

Polyethylene glycolated (PEGylated) liposomes have greater advantages of stable drug entrapment, very low drug leakage for longer period of time, prolonged circulation in the blood and the capability to accumulate in target/tumor tissues through EPR effect [69–71]. The earlier study has reported that modified liposomes coated with Folate-poly(L-lysine) and carrying doxorubicin drug have shown twofold higher cytotoxicity than poly(L-lysine) coated liposomal DXR on KB cells [72]. This might be attributed to the occurrence of folate receptor-mediated endocytosis. Further, the evaluation of Folate receptor targeted liposomes as carriers of a chemotherapeutic drug; Vincristine (F-L-VIN) exhibited a significant receptor-specific cytotoxicity with an IC_{50}value of 2.64 ± 0.14 μM on KB cancer cells compared to non-targeted liposomes [73]. PEGylated liposome loaded with doxorubicin is used in the treatment of different types of cancer and several nanosomes loaded with different drugs such as camptothecin, docetaxel, vitamin D analog and bryostatin-1 have also been developed by Aphios Corp. Woburn, MA 01801, USA and used in the treatment of multiple types of cancer [67].

Several researchers have effectively reported the use of liposomes, dendrimers and polymeric NPs in the combination therapy against cancers [74]. For example, attempts have been made to simultaneously deliver DNA and drugs via liposomes using cationic core–shell NPs, which were synthesized by self-assembling biodegradable amphiphilic copolymers. These ENPs are more advantageous than liposomes, because of their easy fabrication, and manipulation of their size and charges [75]. According to them, the cancer growth was more effectively suppressed by the co-delivery of paclitaxel along with a plasmid encoding for interleukin-12, compared to the individual delivery of paclitaxel or the plasmid as observed in a breast cancer animal model. Likewise, a formulation of combretastatin–doxorubicin nanocell was used to deliver combretastatin and doxorubicin to target lung carcinoma, melanoma and various other cancer types [76]. Such studies were further supported by few novel polymeric nano-formulations, such as poly [lactic-co-glycolic acid] NPs co-encapsulating vincristine and verapamil, polyalkylcyanoacrylate NPs co-encapsulating doxorubicin and cyclosporin A, poly [ethylene glycol]–poly [aspartate hydrazide] block copolymers–Dox–WOR NPs, PDMAEMA–PCL–PDMAEMA-based cationic micelles, against various cancer types [74, 77–79].

Polymer and polymer–drug conjugate NPs for cancer treatment

Polymeric NPs are generally colloidal solid systems and have the capability to dissolve, entrap, encapsulate, and adsorb therapeutic drug onto the constituent polymer

matrix [80]. Polymeric NPs may vary from nanospheres to nanocapsules such as micelle [81], polymerosome [82, 83] dendrimers [84] and hyper-branched polymers [85]. Moreover, natural macromolecules including polysaccharides and polypeptides [86] have also been characterized as drug delivery systems. Different shapes/designs of polymeric ENPs may be attributed to the flexibility provided by polymers.

It is well known that polymeric ENPs have been extensively used in the encapsulation as well as delivery of drugs such as lipophilic and hydrophilic drugs for many years. The unique physical and chemical properties of the polymers, including dispersity index, molecular weight, crystallinity and hydrophobicity helps in the precise control of drug release kinetics and degradation of drugs [67]. Moreover, the surface chemistry of polymeric NPs can be modified and stabilized through conjugation, grafting, or adsorption of other hydrophilic polymer such as PEG, to improve the circulation half-life and also to reduce the hepatic uptake [87, 88]. PEG helps to protect NPs from the reticulo-endothelial system (RES); however, it is known to prevent the cellular uptake as well as intracellular drug release [89].

Modification of polymeric chains through side-chain grafting of chemotherapeutic drugs results in the formation of polymer–drug conjugates. Polymer–drug conjugates helps in the delivery of higher doses of drugs to the target sites. The entry of synthetic polymer–drug, HPMA-doxorubicin [N-(2-hydroxypropyl) methacrylamide] copolymer (PK1), into the phase II clinical trial for advanced breast cancer [90] has been a breakthrough and created a significant interest in the field of cancer therapeutics. Further, the pharmacokinetic study of PK1 has showed a distribution time ($t^{1/2}$) and an elimination ($t^{1/2}$) time of 1.8 and 93 h, respectively. In the Phase I clinical study PK1 exhibited antitumor activity against refractory cancers with maximum-tolerated dose of 320 mg/m^2 and dose-limiting toxicities such as febrile neutropenia and mucositis [90]. Furthermore, several polymer–drug conjugates are in clinical phase and/or recommended for use in cancer therapy which include paclitaxel polymer conjugate (paclitaxel poliglumex) against lung cancer [91], and Oncaspar (PEG–l-asparaginase) for acute lymphoblastic leukemia [92]. Polymer drug conjugates in which drugs are grafted on the side chains of poly-amino acids have also been demonstrated with significant therapeutic efficacy along with high drug loading capability [67, 93, 94]. Moreover, several different linkers have been used to increase the drug loading capacity of polymeric–drug conjugates. It has been reported that the degradable linker, polyglutamate-glycine-camptothecin enhanced the drug loading capacity from 5 to 50%. Further, the use of glycine linker has significantly increased the drug loading capacity compared to polyglutamate-camptothecin alone; this may be due to the reduced steric hindrance by glycine linker [67].

Micelle and dendrimeric NPs for cancer treatment

Micelles are spherical structures with a hydrophobic core formed by amphipathic lipids or other molecules, including poly-amino acids or polymers. Polymeric micelles act as promising and perspective delivery molecules for cancer therapeutic drugs [95]. It has been reported that polymeric micelles ranging in size from 10 to 200 nm are known to enhance the accumulation of drugs within tumor cells due to the EPR effect [96, 97]. Several different micelle NPs have been developed and characterized such as, Genexol-PM, NK105, and Nk911 [67]. However, the first non-targeted polymeric micelle formulation approved for cancer therapy is Genexol-PM. Genexol-PM is a block copolymer micelle formulation of paclitaxel (Taxol) with a size of ~ 60 nm and drug (Paclitaxel) loading capacity of ~ 15% (w/w). It has been reported earlier that Genexol-PM exhibit higher paclitaxel concentration in the tumor tissue than Taxol alone [98]. Genexol-PM, which is in the phase II trial study, has shown antitumor activity in patients with non-small-cell lung cancer at the dose of 230 mg/m^2 with low incidence *y* of toxicity [99]. Polymeric micelles loaded with thioridazine (THZ-MM) and doxorubicin (DOX-MM) have been synthesized and characterized to determine the antitumor activity. The size of these micelles were found to be ~ 89.6 nm (DOX-MM) and ~ 77.0 nm (THZ-MM), respectively, and the co-delivery and/or individual delivery of these micelles had shown significant anticancer activity against breast cancer stem cells [97].

Dendrimers ranges in size from 5 to 10 nm are globular macromolecules possessing well-defined branching architectures. The basic components of dendrimers are central core, branching units and terminal group, the availability of terminal functional groups helps in further surface modifications [100]. Therapeutic agents/drugs can be encapsulated or bound in the internal cavities or on surfaces of the dendrimers through electrostatic and/or hydrophobic interactions or through covalent attachment to the terminal functional groups. The availability of controlled synthetic mechanisms led to the development of different class of dendrimers which find potential applications in diagnostics, drug targeting and also in drug delivery. Several different types of dendrimers have been developed by several research groups such as polyamidoamine (PAMAM), Poly (propylene imine) (PPI), and Poly-L-lysine (PLL) dendrimers. Doxorubicin (DOX) conjugated to carboxyl-terminated PAMAM dendrimers decreased the tumor (lung metastasis) burden in a model and also increased the efficacy of DOX treatment against lung metastasis in mouse model [101]. Further, researchers have developed "avidimers" [67], containing methotrexate polyamidoamine targeted for tumor vasculature [102].

Protein and polymerosome NPs for cancer treatment

Proteins are considered as ideal molecules in the preparation of NPs due to their capability to interact with both solvent and the drug [103]. Moreover, protein-based NPs are biodegradable, less toxic, easily metabolizable, and allow surface modifications for the attachment of ligands and drugs for targeted delivery and efficacy [103, 104]. Several water soluble proteins including albumin, gelatin, elastin, legumin and water insoluble proteins such as zein, gliadin have been explored in the synthesis of NPs and have been characterized as drug delivery carriers in the cancer treatment [103].

Protein-based NPs have made a significant improvement in cancer therapy. Albumin is a natural molecule capable of transporting molecules (no-covalent interactions) across endothelial barriers. Albumin accumulates in the tumor due to its intrinsic targeting abilities and enhanced permeability and retention effect [67]. Several studies have demonstrated the increased uptake of albumin bound paclitaxel in endothelial cells as well as in the extra vascular space [105, 106]. The albumin bound drug NPs such as Abraxane, ABI-008, are albumin-bound paclitaxel are approved by FDA for metastatic breast cancer therapy [67] and ABI-009 is under clinical trial against non-hematologic malignancies [103]. An earlier study showed that albumin-bound paclitaxel NP formulation (ABI-007) has showed maximum-tolerated dose ranging from 100 to 150 mg/m^2, the dose-limiting toxicities observed were neutropenia and peripheral neuropathy [105]. Albumin has been evaluated as a delivery system for the low water solubility drugs such as rapamycin at the concentration of ~2.5 mg/mL [103]. Abraxane in combination with other chemotherapeutics such as vorinostat and rapamycin have been tested against metastatic breast cancer, ovarian and prostate cancer.

Amphipathic polypeptide or synthetic polymers forms polymerosomes or polymer shell vesicles (with a diameter of about ~100 nm) through self-assembly. The morphology of polymerosomic NPs depends on hydrophilicity or hydrophobicity of polymers and structures may be bilayer, spherical, or cylindrical [67, 107]. Moreover, the thickness of the membrane core is determined by the hydrophilic/hydrophobic ratio and size of the di-block copolymer [107]. Polymerosome NPs exhibit significant stability and lateral fluidity and the release of polymerosomes depend on the destabilization and degradation of shell layer and polymer chain, respectively [67]. Ahmed et al. [108] reported that the polymerosome NPs loaded with doxorubicin and paclitaxel with a maximum-tolerated dose of 2.5 mg/kg, exhibited therapeutic effect on breast cancer tumor. Moreover, in comparison to formulations by free drug, the polymerosome NPS reduced tumor size within 5 days post-injection. A nano-dumbbell consisting of hydrophobic NP core and a hydrophilic polymerosome shell has been synthesized to use as transducers in photodynamic therapy [109]. In addition, the lipid shell polymerosomes loaded with zinc (II) phthalocyanine (photosensitizer used photodynamic therapy) was used to minimize corrosion and/or non-specific absorption during transportation [110].

Inorganic NPs for cancer treatment

The development of nanotechnology offered the development of metal and metal based ENPs with potential applications in biomedicine especially targeted drug therapy for cancer. Several inorganic NPs have been developed, characterized and evaluated for use in cancer therapy including AuNPs, AlNPs, CuNPs, and semiconductors such as quantum dots, carbon nanotubes, carbon dots and iron oxide, These molecules have been evaluated for therapeutic and diagnostic purposes in cancer therapy, however, only less number of inorganic ENPs have been translated into clinical practice presently [111]. The characteristic features of quantum dots such as size-dependent luminescence, stability against photo-bleaching and high fluorescence yields allow them to use in a wide range of medical and biological fields including cancer therapy, drug delivery, cell targeting/imaging, fluorescent probes and diagnostics [112]. The EPR effect is difficult to be used for tumor drug delivery due to heterogeneity of tumor vasculature, uptake by the RES and particle detection. However, PEGylation of NPs reduces uptake by RES and increases the EPR effect compared to free drugs [58]. Addition of tumor recognition molecules such as transferrin, epidermal growth factor, monoclonal antibodies, on the surface of NPs helps in the delivery of drugs at the tumor sites. It has been reported that, metal oxide NPs such as cobalt oxide NPs (CoONPs) modified by the addition of *N*-phosphonomethyl iminodiacetic acid (PMIDA) facilitated the binding/conjugation of cancer cell lysate antigen (Ag-PMIDA-CoONPs), These Ag-PMIDA-CoONPs were found to stimulate the immune responses against conjugated cancer lysate antigens only and acts as a antigen delivery system for antitumor vaccine [113], Furthermore, PMIDA-CoO NPs and chitosan-coated CoONPs were also reported to induce apoptosis/cell death through DNA damage, caspase activation and oxidative stress in leukemic cell lines [114, 115].

Inorganic ENPs made of transition metals d-block elements such as Ti, V, Cr, Re, Mn, Au, and Cu have found potential applications in photo activated chemotherapy for cancer and inorganic ENPs based cancer therapy is becoming significant and interesting field [116]. Further, the anticancer activity and photophysics of several inorganic elements such as Ti, V Cu, Fe, Pt, Rh, and Au have been well established [63]. However, further advancement in the characterization of these inorganic NPs and in vitro/in vivo

study on different types of cancers would help in the potential application of these ENPs at the clinic.

Gold nanostructures with a particle size ranging from 2 to 500 nm are generally synthesized from the reduction of $HAuCl_4$ assisted by various reducing/stabilizing agents under the different environmental conditions such as pH, pressure and temperature. The advantages of AuNPs synthesis is that their size and shape can be easily controlled during their synthesis. The ideal size between 1 and 150 nm with varied shape, and possessing distinctive chemical, physical, optical and electrical properties can be obtained readily [117–119]. AuNPs are the most stable materials and exhibit similar properties even when dilutions are changed and usually, they are non-toxic and exhibit both in vitro and in vivo biocompatibility. Because of this reason, they are widely employed in the biomedical applications especially for cancer diagnosis and therapy [120]. The most likely mechanism, by which AuNPs enter the cells, is by non-specific receptor-mediated endocytosis. In particular, AuNPs are effective as thermal destructive agents of cancerous cells owing to their effective photothermal heating capabilities and surface functionalization [121]. The photothermal therapy requires high photothermal conversion efficiency of NPs. The photothermal conversion efficiency of AuNPs depends on structural dimensions such as size and shape [122]. Several different AUNPs have been characterized and their potential applications in diagnosis and treatment of melanoma cancer have been determined [122]. Moreover, AuNPs based platforms have also been employed in the detection of circulating cancer markers such as vesicles, circulating tumor cells, proteins and nucleic acids as well [123]. Furthermore, in a recent study the green synthesized AuNPs were demonstrated with in vitro anticancer activity against MCF-7 cell lines at 74 µg/mL [124].

AuNPs are used in biomedicine as drug carriers, radiosensitizers, and used in thermal therapy for cancers, diagnosis of cancers, and image analysis [119]. Au possess several advantages with synthetic versatility to the unique electronic and optical properties, AuNPs are widely employed for various biomedical applications. AuNPs have the ability to bind to amines and thiols, thus providing a suitable way for introducing several functional groups and may be employed as therapeutic agents when combined with therapeutic drugs or radionuclides, delivering genes/small-interfering RNAs, photo-acoustic imaging, and to target specific sites or proteins [119, 125–129].

In recent years, the available drugs are modified to enhance their pharmacokinetics to reduce non-specific toxicity and enable the delivery of drugs to target tissues at high doses. For instance, 5 nm AuNPs was used as a delivery agent bound with cetuximab as an active targeting agent in treating pancreatic cancers [130]. Likewise, AuNPs complexed with gemcitabine at low doses led to increased tumour growth inhibition (> 80%) in a pancreatic cancer model [130, 131]. Jiang et al. [132] synthesized AuNPs coated with citrate with sizes between 2 and 100 nm. These particles when bound with trastuzumab antibodies enabled to target and cross-link to human epidermal growth factor receptor (HER)-2 in human breast cancer cells. Hyperthermia induces apoptotic cell death and hence, used in cancer therapy in combination with radiotherapy and chemotherapy. AuNPs are very advantageous in this regard and an in vivo study has demonstrated that 100 nm sized Au nanoshells accumulated in human breast cancer cells (SK-BR-3) maximally within 24 h when injected intravenously. Interestingly, applying of laser showed an increase of 37 °C in nanoshell-treated mice, while in control mice there was only 9 °C increase. Also, there was no tissue damage found in the nanoshell group and mice survived up to 90 days without any tumour recurrence symptoms. Similarly, 110 nm sized PEGylated Au nanoshells and laser therapy were found effective in treating human prostate cancer [119, 133–135]. While, AuNPs improve the contrast and structural imaging modalities in Magnetic Resonance Imaging (MRI), positron emission tomography (PET) and computed tomography (CT) analysis and help to diagnose cancers. Molecular imaging studies provide in vivo data on the metabolic functions of cancers and allow easy identification of molecular markers [58, 136]. Most of the AuNPs studies in cancer diagnosis and therapy have shown positive effects. However, more studies are encouraged to investigate on the factors including shape, size, surface coating, and doses, influencing on the functional properties of AuNPs in addition to their observation in animal models.

ENPs and nanocomposites in tissue engineering and regenerative medicine

The development of biomaterials led to the evolution of advanced technology in the field of medicine known as tissue engineering (TE) and regenerative medicine (RM) and has revolutionized the field of medicine.

The fundamental components of TE include biomaterial scaffolds, cells, and signaling biomolecules [137]. Restoration of tissue function and/or repopulation of defect site by TE approach involve implantation of biomaterial scaffolds which are porous, biodegradable and seeded with adequate amount of normal cells [138, 139].

Growth factors (GFs) and differentiation factors (DFs) play a significant role in the proliferation, migration, maturation, and differentiation of functional precursors into mature functional tissues [140]. Hence, the success of RM and TE depend on the accurate presentation of GF's/DF's surrounding the healthy tissue and their concentration on the biomaterials during TE approach [141, 142]. Moreover, the effect

of TE and RM also depends on the availability of effective and controlled release of GF's/DF's.

Several different types of biological nanomaterials including NPs, nanotubes, nanofibers, and fabricated nano-devices lesser than 100 nm dimension having potential applications in cell growth and tissue regeneration have been studied by several research groups. Biological nanomaterials explored in TE and RM must have the capability of eliciting several specific cell to cell interactions such as attachment, adhesion, multiplication, and differentiation. Hence, the selection of biomaterials is the most significant factor in the success of TE approach [143]. Biocompatibility surfaces coupled with suitable mechanical properties constitute the basic and fundamental requirements of biological materials explored in TE and RM. Several such biological materials have been investigated and characterized for use in TE and RM. However, it has been observed that no single biodegradable polymeric material can satisfy the basic and fundamental requirements. Therefore, the combination of biomaterials through addition of inorganic/biomolecules onto biodegradable polymeric matrices is an effective strategy to obtain nanocomposites having multifunctional and specific activity [143]. Several different polyester based nano composite materials have been developed to use in medical applications. The natural polymeric substances such as, silk [144], starch [145] and collagen [16] have been characterized for their potential application in medicine.

The advanced technology exploring the scaffolds and NPs loaded with bioactive agents has grown significantly which in turn led to the advancement in the field of TE and RM. The intended application of scaffold determines its composition and physical parameters. Many different natural and synthetic polymers have been characterized and used as TE scaffolds [138, 139]. The most commonly used TE scaffolds based natural polymers are gelatin, fibrin, collagen, polyhydroxyalkanoates, hyaluronic acid, chitosan and alginate [142]. Whereas, PLGA, PGA, PLA, PCL, PEG, PEG derivatives (poly (fumarate)) PEG copolymers such as poly (amido-amines), poly (vinyl alcohol), orpoly (urethanes) constitute the synthetic polymers used in TE scaffolds.

Several inorganic materials including cement, bioactive glass, calcium phosphate ceramics and ceramic/polymer composites have also been developed and found their application in bone TE [146, 147]. Many different conventional and advanced techniques have developed for the preparation of biological scaffolds used in TE approach which include melt molding, fiber bonding, solvent casting, gas foaming, particulate leaching, rapid prototyping phase separation, electrospinning, nanofabrication. Moreover, the surface-patterning techniques such as nano-imprint lithography, electron-beam lithography, photolithography, nano-contact and printing, have also been developed in the preparation of effective TE scaffolds. However, among all electrospinning is the most common and versatile technique used in the preparation of TE scaffolds having high surface area to volume ratio [40, 148]. Different ENPs coupled scaffolds have been characterized for use in bone and cartilage TE and RM.

ENPs and nanocomposites in drug delivery

The ENPs are capable of delivering the drug/bioactive agents in a controlled manner. Transient and sustained delivery of bioactive agents to the target/specific site is a major challenge in TE and RM approach. The controlled and sustained release of drug/bioactive agent by the ENPs provides several advantages which include protection of therapeutic molecule from degradation, maintenance of drug/bioactive agent concentration, along with targeted delivery and reduced side effects. Hence, the therapeutic efficacy of a drug/bioactive agent increases with the development of effective delivery systems, in this regard NPs acts as a promising device [38, 39]. However, an ideal NP carrier should be stable, biodegradable, non-immunogenic, and capable of releasing the drug/bioactive agent only at the target site in a cost-effective manner [149, 150]. The role of ENP's in drug delivery has been well established and play significant and crucial role even in TE and RM also [140]. NPs are required to cross the physiological barriers of the system depending upon the application, target cells and route of administration [151]. Hence, the success and also the efficiency of NPs-based delivery system depends on the capability of transporting loaded bioactive agent through physiological barriers to reach the target site for optimum pharmacological activity. ENPs are internalized through different mechanisms such as phagocytosis, endocytosis, pinocytosis depending on the type of NPs and drug conjugate system.

The cell viability and internalization property varies from one cell type to another. Moreover, other parameters including composition, surface charge, size and concentration of NPs, and also incubation time influences the cell viability and internalization efficiency of NPs by the cell [40]. NPs based drug/bioactive agent delivery can be carried out through encapsulation using nanospheres developed from biodegradable (natural/synthetic) or non-degradable polymers. Poly(L-lactide) (PLA) or poly(L-lactide-co-glycolic) (PLGA) [152, 153] are the best examples for synthetic biodegradable NPs, while proteins and polysaccharides such as, collagen, gelatin, fibrin, alginate, and chitosan can be used as natural biodegradable polymers for NPs synthesis. Metals and metal oxides/sulfides such as, gold, hydroxyapatite, alumina and silica [154–157] constitute non-degradable NPs. The selection of polymeric material for the construction of NPs for delivery system depends on many factors including, size, surface chemistry and charge of the NPs, characteristic features of the dug/bioactive agent, dug/bioactive agent release profile, and also the biodegradability and

biocompatibility of NPs [158]. The ENPs synthesized from biodegradable materials exhibit significant biocompatibility with negligible immunogenicity, apart from degradability.

The application of ENPs/nanocomposites in drug/bioactive agent delivery may improve the effective treatment of many diseases; one such is the cancer targeted drug delivery. Targeted drug delivery may be passive, active or physical targeting of cells, tissues, organs and even organelles. Organelle targeting drug delivery is an emerging and promising field of research due to its application in cancer therapy.

The passive targeting is based EPR effect (Sect. 2.1), is known to be influenced by several parameters including the shape, size, and surface charge of NPs which in turn influences penetration speed, circulation time, and also intracellular internalization mechanism [159, 160]. The surface properties of NPs could play significant role in their circulation in the blood vascular system and subsequent internalization by the cells [150]. Cancer cells tend to take up NPs with positive charge more readily than negatively charged NPs because of their negative charge on the surface [150]. Moreover, the geometry of NPs also influences the cellular uptake. Further, Li et al. established that internalization rate of PEGylated NPs spheres is faster compared to cubes, however, rods and disks exhibited slowest internalization rate [161]. Many different NP structures in which drugs are dissolved, entrapped, and/or conjugated on to the surface have been developed and several of them have received clinical approval and approved by FDA for instance; liposome mediated doxorubicin and daunorubicin delivery system, an albumin-bound NPs containing paclitaxel, abraxane against breast cancer [162].

However, active targeting is selective and can react only with target cells. In this process the NPs are functionalized with a ligand which has significant affinity towards molecule abundant on cancer cells. This increases the uptake specificity, delivery efficiency of NPs and sometimes protects the drug from enzymatic digestion. Active targeting mechanism directs the drug to a specific cell, organ, or organelle and can alter the normal distribution patterns of a carrier; however, passive targeting rely on the EPR effect and natural distribution of the drug [150]. Physical targeting involves navigation of drugs to the target site using external stimulation factors, such as magnetic fields and/or radiation such as photothermal therapy.

Several NP based photothermal agents have been tested in cancer therapy such as, AuNPs, graphene, carbon nanotubes. Several different mechanisms such as pH, heat and fictionalization/conjugation of NPs with polymer or PEG have been explored in the delivery of drugs. For instance, carbon nanotubes and graphene oxide conjugated with polymer is pH sensitive and kill cells photothermally [163], while graphene nanosheet coated with silica and functionalized with PEG have been reported to deliver doxorubicin [164]. The heat energy produced from MNPs due to their oscillation in a magnetic field is also explored in the cancer treatment (magnetic hyperthermia). However, the therapeutic effect and production of heat energy depend on distance between target cell and MNPs, strength of the magnetic field and sensitivity of target cell to magnetic field. Biological polymers such as, carbohydrates and proteins are coated onto MNPs to protect them against potential toxin release and corrosion. The imaging capabilities of MNPs offer great potentials in delivering MNPs based drug carriers to the target site (precision oncology), which in turn allows evaluation of distribution of the drug carrier and noninvasive imaging [45].The MNPs are mainly based on cobalt, nickel, magnetite (Fe_3O_4) or maghemite. However, iron oxides are most commonly employed due to its shape controllability and biological compatibility [150]. An earlier study showed that, iron oxide NPs obtained in the size of ~ 100 nm were found to be biocompatible and effective carrier for targeted drug delivery to cancer cell lines [165]. Many clinical trials have been conducted both in vivo and in vitro by photothermal therapy and also by magnetic hyperthermia [166]. It has also been reported that combinatorial effect of photothermal therapy and magnetic hyperthermia promotes effective internalization of NPs by tumor cells, rather than individual effect [167]. MNPs have potential significant applications in the field of in vivo human diagnostics and drug delivery and are already been used in the transportation of antimicrobial agents and anticancer drugs [168].

ENPs in biomolecules detection

Over the past few years, nanoscience and nano-biotechnological research advancements have focused towards the application of nanotechnology in biomolecular detection [135, 169]. The ENPs have significantly played a significant role in biomolecules detection. In specific, they have replaced the conventional molecular techniques and improved the sensitivity and accuracy of the identification. The thermal, optical, physical and electrochemical techniques have certainly improved in recognizing the molecules in solution when observed in the biosensing devices. NPs are widely used in developing new sophisticated sensing devises and assays which can improve the identification of nucleic acids and proteins [169, 170]. Several types of NPs including AuNPs, MNPs, quantum dots, silica NPs, inorganic phosphor NPs have been used in detecting viruses, hormones, specific antigens, thyroid-stimulating factors, DNA and other biomolecules [169, 171]. The physiological changes in the cell such as change in the type and concentration of metabolites may takes place due to pathological/disease condition or disorder, hence, the diagnosis of the disease and identification of its related physiological changes such as sensing and monitoring of the intracellular pH helps in understanding the disease

biology [172]. Several nanoscale metal organic frame works (nMOFs) have been developed for the detection of several physiological changes in living cells, such as sensing the real time intracellular pH [173], intracellular oxygen quantification [174], and sensing nitric oxide concentration [175].

The advancement in the field of nanotechnology and development of novel NPs employed in the biomolecular detection could be a major breakthrough in the field of medicine which helps in the detection and diagnosis of many diseases which are still undetectable in the early stage such cancer through convention diagnostics. The availability of such advanced biomolecular diagnostics helps in the improvement of disease management along with the improvement in patient's quality life.

ENPs and nanocomposites as antimicrobial agents

The improper or misuse of antimicrobials have caused the resistance property in microorganisms and is a present global challenge and causing a great threat to the patients infected with pathogenic microbes [2].There is a rise in the number of drug-resistant bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci which is a challenge to the medical practitioners..

Recent advancement in the area of nanobiotechnology has made the possibility of synthesizing nano-range molecules with incredible applications in the field of biomedicine and therapeutics. Further, these nanoscale nanocomposites possess excellent antimicrobial properties against various resistant microbes [2]. Hence, the antimicrobial property of ENPs can be employed as alternatives in treatment of drug-resistant microbes in the medical field. The possible mechanisms of antimicrobial action by ENPs are represented in Fig. 3 and Table 1.

Several inorganic NPs including silver NPs (AgNPs) have exhibited antimicrobial activity against diverse microbes. Silver ions have more affinity towards sulfur and phosphate groups and this might be significant in its antimicrobial activity. Silver ions (Ag^+) released from NPs reacts with the proteins with sulphur components on the cell membrane. Ag^+ produces ROS within the cell and are one of the main cause for cell death [176].The size of NPs is the key factor in deciding their efficacy against microbes. The size of < 10 nm produces holes/pores on cell membrane resulting in cell leakage and eventually will lead to microbial cell death [176, 177]. The minimum inhibitory concentration (MIC) values of AgNPs against pathogenic microbes differ with the type and sizes of the nanoparticles [2].

The biosynthesized AgNPs have been investigated against several pathogens with superior inhibitory potential [21, 178–184]. The AgNPs synthesized using *Andrographis paniculata* leaf extract exhibited higher antibacterial activity against Gram positive *Enterococcus faecalis* strains. Further, the surface zeta potential study revealed the key role of cell surface charge in bactericidal activity [185]. Further, the AgNPs synthesized using leaf extract of *Ocimum gratissimum* exhibited bactericidal activity against *E. coli* and *S. aureus* through ROS mediated cell surface damage [186]. Similarly, the surface of MgONPs has typically high pH and when bacterial cells interact with MgONPs, the high alkaline pH damages the cell membrane which is also called as alkaline effect [187–189]. Further, the antibacterial effect of MgONPs also depends on their size. The MgONPs less than 15 nm are known to exhibit superior bactericidal activity [187, 190]. MgONPs are effective against both Gram-negative and Gram-positive bacterial strains [191, 192]. In

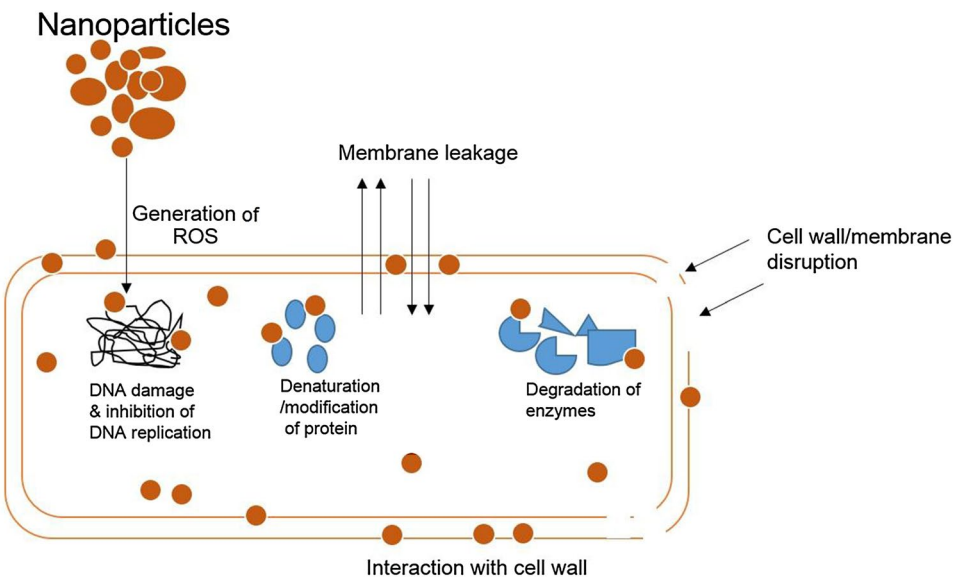

Fig. 3 Mode of action of engineered nanoparticles against microorganisms

another study, it has been shown that MgONPs were effective against *E. coli* (MIC; 500 µg/mL), *S. aureus* (MIC; 1000 µg/mL), and *Pseudomonas aeruginosa* (MIC; 1000 µg/mL) [193]. Titanium dioxide inhibits bacterial strains by releasing ROS. In particular, the crystal surface of TiO_2 interacts with fluids or water through photocatalytic reaction that generates the hydroxyl free radicals. The release of ROS then causes site specific DNA damages [2, 194–197]. ZnONPs show antimicrobial activity by generating hydrogen peroxides, and releasing Zn^{2+} ions. Also, ZnONPs release ROS including H_2O_2, OH^-, and O_2^{2-}. These ROS effectively damage the bacterial cell growth [198, 199]. The generation of hydrogen peroxides increases with the increased surface area of ZnONPs [2]. ZnONPs are shown to inhibit several kinds of Gram-negative and Gram-positive bacterial strains and are very effective against food borne pathogens [200, 201]. The inhibitory potential of iron oxide NPs is due to generation of singlet oxygen ($^1O_2$), superoxide radicals (O^{2-}), hydroxyl radicals (OH^-), and hydrogen peroxide (H_2O_2).

AuNPs were shown to possess anti-cancerous and antibacterial activity through photo thermal heating [21]. AuNPs and toluidine blue O (photosensitizer) have exhibited a synergistic antimicrobial activity against methicillin-resistant *Staphylococcus aureus* [202–205]. The bioactive molecules including antimicrobials, carbohydrates, antibodies, proteins, and oligonucleotides may be capped with AuNPs for better biological activities [206, 207], For example, the addition of vancomycin (antibiotic) to kill vancomycin-resistant enterococci [208, 209] and aminoglycosidic antibiotics to act against various bacterial pathogenic strains [210, 211]. AuNPs act on the bacterial cell by generating holes/pores in the cell wall/membrane and inhibit the transcription process through preventing the DNA uncoiling [212]. Several studies have reported the antimicrobial properties of copper (Cu) NPs (CuNPs) against several bacterial strains including Gram-positive *Bacillus subtilis* and *S. aureus* [213]. CuNPs produced through the biological process have been reported to possess higher inhibitory potential against drug-resistant human pathogens such as *S. aureus* and *E.coli* [214]. The antimicrobial property of CuNPs is due to their effective adhesion/attachment to the bacterial cell walls and causing the cell architecture damages [215]. Moreover, CuNPs have greater affinity towards carboxyl and amine groups found on *B. subtilis* cell surface and hence, they are highly effective against these strains [2].Copper ions released are reported to have the potential to disrupt biochemical processes inside bacterial cells [216] may also intercalate with nucleic acid strands and interact with DNA molecules. The mechanism of antimicrobial of AlNPs is due to the disruption of cell walls leading to cell death through ROS generated from the NPs [216]. However, aluminum NPs are regarded as scavengers of free radicals and appear to protect cells from the death due to oxidative stresses. However, this property is size independent and might depend upon the structure of the particles [2, 217]. Bismuth (Bi) NPs (BiNPs) are reported to function against several microbes. A study by Hernandez et al. [117, 218] reports the antibacterial and antifungal activity of BiNPs at <1 and 2 mM concentrations, respectively. The BiNPs were reported to inhibit the drug-resistant bacterial strain, *Helicobacter pylori* significantly [219]. The mechanism of action was due to the inhibition of the bacterial growth by altering the amino acid metabolism and Krebs cycle [220]. Carbon nanotubes are shown to be effective against Gram-positive and Gram-negative bacterial strains including *Salmonella enterica*, *E. coli*, and *Enterococcus faecium*. Moreover, carbon NPs when complexed with silver inhibit multidrug-resistant microbes such as *Acinetobacter baumannii*, *K. pneumonia, S. aureus*, and *Yersinia pestis* [2, 221]. They cause cell wall disruption and DNA damages [222, 223]. Fullerenes, a soccer ball shaped carbon NPs have been investigated and showed antimicrobial activity against *Salmonella spp.*, *E. coli, Shewanella oneidensis* and *Streptococcus* species [224–226]. Likewise, graphene oxides were also shown to effectively inhibit *E. coli* and *S. aureus* [227].

The organometallic polymers were reported to have effective inhibitory effect on several microbes. Experimental study has showed that peptide (lysine and phenylalanine) based NPs exhibit higher antimicrobial potential against *P. aeruginosa, E. coli, Serratia marcescens* and *Candida albicans* [2, 228]. Several different nanocomposites have been prepared and characterized for antibacterial activity for instance, AgNPs-graphene oxide (Ag NPs/GO) composites exhibited antibacterial activities against *E. coli* and *S. aureus* [43].Ag NPs decorated on thiol (-SH) grafted GO layers exhibited inhibitory effect against *S. aureus* and *P. aeruginosa* [42] and Ti substrates surface modified by GO thin film and AgNPs against *Porphyromonas gingivalis* and *Streptococcus mutans* [41]. Likewise, quaternary ammonium compounds are shown to inhibit microbes by interacting with the bacterial cell membrane. They cause cell membrane pores and denatures cellular proteins/enzymes [2, 229]. Polymers such as polysiloxane and triclosan are reported to possess superior activities against *E. coli* and *S. aureus* and *Corynebacterium spp.,* respectively [230, 231].

Nanotechnology bids an excellent opportunity to inhibit viral multiplication and their global spread [2]. AgNPs have shown to possess antiviral properties against Hepatitis-B, HIV-1 (human immunodeficiency virus 1), HSV 1 (herpes simplex virus type 1) and monkeypox virus [2, 232, 233]. AgNPs exert antiviral activities by acting as a virucidal agent or by inhibiting the entry of virus particularly at early stage of viral replication. Also, NPs are reported to inhibit viral particles by binding on to their cell surfaces. After binding, they alter or denature the viral proteins [2]. AuNPs have also been reported to exhibit anti-HIV activity and with

different anionic groups can inhibit influenza virus. The negatively charged AuNPs exhibit inhibitory effect against several influenza strains; this may be ascribed to the prevention of viral attachment. AgNPs capped with mercaptoethane sulfonate effectively inhibited HSV 1 infection [21]. These NPs prevent the infection by hindering the virus entry into the cell. The Au/Cu sulfide core/NPs shell system has shown antiviral activity against norovirus virus-like particles [234]. Likewise, TiO_2, poly-L-lysine (PL), and DNA/RNA nanocomposite was shown to inhibit influenza A virus [235]. The surface modified NPs potentially inhibited viral infections [236]. More recently, NPs functionalized with zanamivir showed an effective activity against H1N1 influenza virus through apoptosis process [237]. Likewise, previously, it has been reported that AgNPs inhibit the replications in several viral particles such as herpes simplex virus, dengue virus 2, respiratory syncytial virus, parainfluenza virus 3, bean yellow mosaic virus, and H3N2 influenza [237, 238]. Fungal infections have tremendous contribution in increasing the mortality of immunocompromised patients [2]. Many investigations have showed that the NPs potential against fungi and fungal spores. The antifungal activity varies with particle sizes or zeta potentials. Zeta potential is believed to interact with negatively charged microbial surface and function as antifungal agents. Chitosan NPs are reported to have inhibitory effect on *Candida albicans* and *Fusarium solani*. The inhibitory effect may be credited to the occurrence of negatively charged sialic acid residues in cell the wall. Moreover, AgNPs also exhibit antifungal activity against *C. albicans* and *Saccharomyces cerevisiae* [2]. The synthesized amphotericin B-silver hybrid NPs have significantly inhibited the growth of *C. albicans*, *F. culmorum* and *Aspergillus niger* species [239]. Further, amphotericin B-copper (II) complex exhibited enhanced therapeutic potential against *C. albicans, C. parapsilosis* and *A. niger* [240]. Likewise, CuNPs synthesized chemically have shown antifungal activity against *Fusarium* spp [241]..

Limitations

The NPs can be synthesized by several ways such as, chemical, biological, mechanical method by milling and grinding technology, and gas phase synthesis. In most of these synthetic processes the size of the NPs does not exceed 100 nm. Furthermore, the chemical methods are not eco-friendly; however, the biological methods do not lead the production of any toxic agents and are eco-friendly [242]. The contact of ENPs with living cells/tissues is affected by various factors including their shape, size, and composition. The strong permeability of ENPs is a pre-requisite for its potential application as antimicrobial agent or an agent in drug delivery. Most of the synthesized NPs can penetrate membrane barriers and diffuse in the body. However, there are some possible health hazards of ENPs when they accumulate in cells, tissues and other cellular structures [2]. Synthesis and exposure of NPs with a diameter less than 100 nm may result in adverse side effect; however, the risk linked to NPs varies depending on NPs type [3, 201, 243]. The reactive oxygen species generated by NPs are major contributors in inflammation and toxicity, inducing oxidative stress, apoptosis and activation of signaling pathways. The NPs might escape the body's defense mechanisms because of their nanoscale size and might result in toxic responses and inflammation [2, 3].

Several studies have reported the relationship between pulmonary inflammation and toxicity responses to ultrafine particles [2, 4]. Further, the consequence of ENPs on biological systems is not completely acknowledged. Therefore, complete understanding on the harmful effects/limitations on the use of NPs has to be addressed. Although intrinsic properties NPs offer lot of advantages some of those intrinsic characteristic features poses difficulties also. For example, the high surface area, of NPs favor particle agglomeration followed by formulation instability due to high surface Gibbs energy, and it is highly challenging to prevent [244]. Moreover, the independent control of these intrinsic parameters is also difficult and they might also influence stability issues including sedimentation [245]. Hence, it is difficult to generalize the protocols for NPs synthesis and for optimal cellular uptake. Moreover, it is highly essential to evaluate the potential negative impacts on environment as well as ecological systems due to the production of NPs in a larger scale. Furthermore, there may be unintended exposure of NPs by humans due to their bioavailability in different ecosystems and capability to move along the food webs [246]. Hence, thorough evaluation and regulation is required before the production of NPs in larger scale and also about their utility in biomedical fields.

Conclusion

The advent of nanotechnology and its allied fields revolutionized the field of medicine. Development of NPs represents an exciting, reliable and promising advancement in the field of medicine and biology. The potential application and use of ENPs in the treatment of wide range of bacterial, viral and fungal diseases, cancer therapy, drug delivery, tissue engineering, regenerative medicine, diagnostics, imaging and biomolecules detection has a significant effect on patient care and treatment. The development of advanced and effective ENPs and their applications in cancer treatment would help in overcoming the shortcomings of conventional cancer therapy and may provide a ray of hope for cancer patients in future. The rise of drug resistance property by microorganisms is another great threat, concern and challenge to

the medical practitioners, which could also be overcome through advanced ENPs. The advancement of cutting edge nanomedicine offered the possibility and fascinating opportunities in NPs based bioimaging, early detection of diseases and targeted drug delivery for enhanced therapy. Various ENPs are shown to be effective against several pathogenic microorganisms, and are explored in cancer therapy, TE, RM, diagnostics and biomolecules detection. However, the effectiveness of ENPs in various fields of medicine and biology depends on the type of NPs, their size, stability, and composition. Though, ENPs possess numerous biological activities, their utilization is limited due to the facts such as toxicity, non-degradability, biocompatibility which may cause serious health risks. However, these limitations can be overcome through the use of eco-friendly approaches for NPs synthesis and is well appreciated also. Therefore, more studies are required to prove the effective utility of NPs in various fields of medicine and biology.

Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

References

1. Feynman RP (1992) There's plenty of room at the bottom [data storage]. J Microelectromechanical Syst 1:60–66
2. Rudramurthy GR, Swamy MK, Sinniah UR, Ghasemzadeh A (2016) Nanoparticles: alternatives against drug-resistant pathogenic microbes. Molecules 21:836
3. Choi J, Wang NS (2011) Nanoparticles in biomedical applications and their safety concerns. In: Fazel R (ed) Biomedical engineering–from theory to applications. InTech, Maasticht, pp 299–314
4. Gwinn MR, Vallyathan V (2006) Nanoparticles: health effects—pros and cons. Environ Health Perspect 114:1818
5. Xia Tian, Li Ning, Nel AE (2009) Potential health impact of nanoparticles. Annu Rev Public Health 30:137–150
6. Grillo R, Rosa AH, Fraceto LF (2015) Engineered nanoparticles and organic matter: a review of the state-of-the-art. Chemosphere 119:608–619
7. Bhatia S (2016) Nanoparticles types, classification, characterization, fabrication methods and drug delivery applications. Natural Polymer Drug Delivery Systems Springer, 33–93
8. Pangi Z, Beletsi A, Evangelatos K (2003) PEG-ylated nanoparticles for biological and pharmaceutical application. Adv Drug Del Rev 24:403–419
9. Hett A (2004) Nanotechnology: small matter. Many unknowns Swiss Reinsurance Company, Zurich
10. Banerjee (2001) Liposomes: applications in medicine. J Biomater Appl 16:3–21
11. Yang L, Webster TJ (2009) Nanotechnology controlled drug delivery for treating bone diseases. Expert Opin Drug Deliv 6:851–864
12. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE (2001) Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release 70:1–20
13. Reis CP, Neufeld RJ, Ribeiro AJ, Veiga F (2006) Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles. Nanomed Nanotechnol Biol Med 2:8–21
14. Adams ML, Lavasanifar A, Kwon GS (2003) Amphiphilic block copolymers for drug delivery. J Pharm Sci 92:1343–1355
15. Gillies ER, Frechet JM (2005) Dendrimers and dendritic polymers in drug delivery. Drug Discov Today 10:35–43
16. Lee P, Lin R, Moon J, Lee LP (2006) Microfluidic alignment of collagen fibers for in vitro cell culture. Biomed Microdevice 8:35–41
17. Verma A, Stellacci F (2010) Effect of surface properties on nanoparticle–cell interactions. Small 6:12–21
18. Skandalis N, Dimopoulou A, Georgopoulou A, Gallios N, Papadopoulos D, Tsipas D et al (2017) The effect of silver nanoparticles size, produced using plant extract from *Arbutus unedo*, on their antibacterial efficacy. Nanomaterials 7:178
19. Whitesides GM (2005) Nanoscience, nanotechnology, and chemistry. Small 1:172–179
20. Hajipour MJ, Fromm KM, Ashkarran AA, de Aberasturi DJ, de Larramendi IR, Rojo T et al (2012) Antibacterial properties of nanoparticles. Trends Biotechnol 30:499–511
21. Rai VR, Bai AJ (2011) Nanoparticles and their potential application as antimicrobials. Formatex, Mysore
22. Ganta S, Devalapally H, Shahiwala A, Amiji M (2008) A review of stimuli-responsive nanocarriers for drug and gene delivery. J Control Release 126:187–204
23. Motornov M, Roiter Y, Tokarev I, Minko S (2010) Stimuli-responsive nanoparticles, nanogels and capsules for integrated multifunctional intelligent systems. Prog Polym Sci 35:174–211
24. Bessa PC, Machado R, Nürnberger S, Dopler D, Banerjee A, Cunha AM et al (2010) Thermoresponsive self-assembled elastin-based nanoparticles for delivery of BMPs. J Control Release 142:312–318
25. Matsuo T, Sugita T, Kubo T, Yasunaga Y, Ochi M, Murakami T (2003) Injectable magnetic liposomes as a novel carrier of recombinant human BMP-2 for bone formation in a rat bone-defect model. J Biomed Mater Res A 66:747–754
26. Tanaka H, Sugita T, Yasunaga Y, Shimose S, Deie M, Kubo T et al (2005) Efficiency of magnetic liposomal transforming growth factor-beta 1 in the repair of articular cartilage defects in a rabbit model. J Biomed Mater Res A 73:255–263
27. Herbst SM, Klegerman ME, Kim H, Qi J, Shelat H, Wassler M et al (2009) Delivery of stem cells to porcine arterial wall with echogenic liposomes conjugated to antibodies against CD34 and intercellular adhesion molecule-1. Mol Pharm 7:3–11
28. Moura V, Lacerda M, Figueiredo P, Corvo ML, Cruz ME, Soares R et al (2012) Targeted and intracellular triggered delivery of therapeutics to cancer cells and the tumor microenvironment: impact on the treatment of breast cancer. Breast Cancer Res Treat 133:61–73
29. Dai Y-Q, Qin G, Geng S-Y, Yang B, Xu Q, Wang J-Y (2012) Photo-responsive release of ascorbic acid and catalase in CDBA-liposome for commercial application as a sunscreen cosmetic. RSC Adv 2:3340–3346
30. Adibkia K, Omidi Y, Siahi MR, Javadzadeh AR, Barzegar-Jalali M, Barar J et al (2007) Inhibition of endotoxin-induced uveitis by methylprednisolone acetate nanosuspension in rabbits. J Ocul Pharmacol Ther 23:421–432
31. Tiwari PM, Vig K, Dennis VA, Singh SR (2011) Functionalized gold nanoparticles and their biomedical applications. Nanomaterials 1:31–63
32. Zinjarde S (2012) Bio-inspired nanomaterials and their applications as antimicrobial agents. Chron Young Sci 3:74–81
33. Bahrami K, Nazari P, Nabavi M, Golkar M, Almasirad A, Shahverdi AR (2014) Hydroxyl capped silver–gold alloy

nanoparticles: characterization and their combination effect with different antibiotics against *Staphylococcus aureus*. Nanomed J 1:155–161
34. Dizaj SM, Mennati A, Jafari S, Khezri K, Adibkia K (2015) Antimicrobial activity of carbon-based nanoparticles. Adv Pharm Bull 5:19
35. Nam J-M, Thaxton CS, Mirkin CA (2003) Nanoparticle-based bio-bar codes for the ultrasensitive detection of proteins. Science 301:1884–1886
36. Chen H, Kou X, Yang Z, Ni W, Wang J (2008) Shape-and size-dependent refractive index sensitivity of gold nanoparticles. Langmuir 24:5233–5237
37. Osterfeld SJ, Yu H, Gaster RS, Caramuta S, Xu L, Han S-J et al (2008) Multiplex protein assays based on real-time magnetic nanotag sensing. Proc Natl Acad Sci 105:20637–20640
38. Hillaireau H, Couvreur P (2009) Nanocarriers' entry into the cell: relevance to drug delivery. Cell Mol Life Sci 66:2873–2896
39. Kim BYRJ, Chan WC (2010) Nanomedicine. N Engl J Med 363:2434–2443
40. Monteiro N, Martins A, Reis RL, Neves NM (2015) Nanoparticle-based bioactive agent release systems for bone and cartilage tissue engineering. Regen Ther 1:109–118
41. Jin J, Zhang L, Shi M, Zhang Y, Wang Q (2017) Ti-GO-Ag nanocomposite: the effect of content level on the antimicrobial activity and cytotoxicity. Int J Nanomed 12:4209
42. Vi TTT, Rajesh Kumar S, Rout B, Liu C-H, Wong C-B, Chang C-W et al (2018) The preparation of graphene oxide-silver nanocomposites: the effect of silver loads on Gram-positive and Gram-negative antibacterial activities. Nanomaterials 8:163
43. Huang L, Yang H, Zhang Y, Xiao W (2016) Study on synthesis and antibacterial properties of Ag NPs/GO nanocomposites. J Nanomater. https://doi.org/10.1155/2016/5685967
44. Han C, Romero N, Fischer S, Dookran J, Berger A, Doiron AL (2017) Recent developments in the use of nanoparticles for treatment of biofilms. Nanotechnol Rev 6:383–404
45. El-Boubbou K (2018) Magnetic iron oxide nanoparticles as drug carriers: preparation, conjugation and delivery. Nanomedicine 13:929–952
46. Chakraborty AK, Roy T, Mondal S (2016) Development of DNA Nanotechnology and uses in molecular medicine and biology. Insights Biomed 1:2
47. Yazdi MH, Sepehrizadeh Z, Mahdavi M, Shahverdi AR, Faramarzi MA (2016) Metal, metalloid, and oxide nanoparticles for therapeutic and diagnostic oncology. Nano Biomed Eng 8:246–267
48. Chidambaram M, Manavalan R, Kathiresan K (2011) Nanotherapeutics to overcome conventional cancer chemotherapy limitations. J Pharm Pharm Sci 14:67–77
49. Vinogradov S, Wei X (2012) Cancer stem cells and drug resistance: the potential of nanomedicine. Nanomedicine 7:597–615
50. Derya İlem-Özdemir EG, Ekinci M, Aşikoğlu M (2016) Nanoparticles: from diagnosis to therapy. Int J Med Nano Res 3:15
51. Subbiah R, Veerapandian M, Yun SK (2010). Nanoparticles: functionalization and multifunctional applications in biomedical sciences. Curr Med Chem 17:4559–4577
52. Nguyen KT (2011) Targeted nanoparticles for cancer therapy: promises and challenge. J Nanomedic Nanotechnol. https://doi.org/10.4172/2157-7439.1000103e
53. Banerjee D, Sengupta S (2011) Nanoparticles in cancer chemotherapy. Prog Mol Biol Transl Sci 104:489–507
54. Gmeiner WH, Ghosh S (2014) Nanotechnology for cancer treatment. Nanotechnol Rev 3:111–122
55. Bae YH, Park K (2011) Targeted drug delivery to tumors: myths, reality and possibility. J Control Release 153:198
56. Sun T, Zhang YS, Pang B, Hyun DC, Yang M, Xia Y (2014) Engineered nanoparticles for drug delivery in cancer therapy. Angew Chem Int Ed 53:12320–12364
57. Maeda H (2001) The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. Adv Enzyme Reg 41:189–207
58. Jain S, Hirst D (2012) O'sullivan J. Gold nanoparticles as novel agents for cancer therapy. Br J Radiol 85:101–113
59. Matsumura Y, Maeda H (1986) A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Can Res 46:6387–6392
60. Fang M, Chen J-H, Xu X-L, Yang P-H, Hildebrand HF (2006) Antibacterial activities of inorganic agents on six bacteria associated with oral infections by two susceptibility tests. Int J Antimicrob Agents 27:513–517
61. Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC (2014) Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. Adv Drug Deliv Rev 66:2–25
62. Yin H, Liao L, Fang J (2014) Enhanced permeability and retention (EPR) effect based tumor targeting: the concept, application and prospect. JSM Clin Oncol Res 2:1010
63. Bhattacharyya S, Kudgus RA, Bhattacharya R, Mukherjee P (2011) Inorganic nanoparticles in cancer therapy. Pharm Res 28:237–259
64. Stylianopoulos T, Wong C, Bawendi MG, Jain RK, Fukumura D (2012) Multistage nanoparticles for improved delivery into tumor tissue. Methods Enzymol 508:109–130
65. Deshpande PPBS, Torchilin VP (2013) Current trends in the use of liposomes for tumor targeting. Nanomedicine 8:1509–1528 **(Lond)**
66. Huwyler J, Drewe J, Krähenbühl S (2008) Tumor targeting using liposomal antineoplastic drugs. Int J Nanomed 3:21
67. Alexis F, Pridgen EM, Langer R, Farokhzad OC (2010) Nanoparticle technologies for cancer therapy. In: Schäfer-Korting M (ed) Drug delivery. Handbook of experimental pharmacology, vol 197. Springer, Berlin, Heidelberg, pp 55–86
68. Voinea M, Simionescu M (2002) Designing of 'intelligent'liposomes for efficient delivery of drugs. J Cell Mol Med 6:465–474
69. Needham D, McIntosh T, Lasic D (1992) Repulsive interactions and mechanical stability of polymer-grafted lipid membranes. Biochimica et Biophysica Acta (BBA)-Biomembr 1108:40–48
70. Unezaki S, Maruyama K, Takahashi N, Koyama M, Yuda T, Suginaka A et al (1994) Enhanced delivery and antitumor activity of doxorubicin using long-circulating thermosensitive liposomes containing amphipathic polyethylene glycol in combination with local hyperthermia. Pharm Res 11:1180–1185
71. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K (2000) Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. J Control Release 65:271–284
72. Watanabe K, Kaneko M, Maitani Y (2012) Functional coating of liposomes using a folate–polymer conjugate to target folate receptors. Int J Nanomed 7:3679
73. Liu Y, Xu S, Teng L, Yung B, Zhu J, Ding H et al (2011) Synthesis and evaluation of a novel lipophilic folate receptor targeting ligand. Anticancer Res 31:1521–1525
74. Parvanian S, Mostafavi SM, Aghashiri M (2017) Multifunctional nanoparticle developments in cancer diagnosis and treatment. Sens Bio-Sensing Res 1:81–87
75. Wang Y, Gao S, Ye W-H, Yoon HS, Yang Y-Y (2006) Co-delivery of drugs and DNA from cationic core–shell nanoparticles self-assembled from a biodegradable copolymer. Nat Mater 5:791
76. Sengupta S, Eavarone D, Capila I, Zhao G, Watson N, Kiziltepe T et al (2005) Temporal targeting of tumour cells

and neovasculature with a nanoscale delivery system. Nature 436:568
77. Zhu C, Jung S, Luo S, Meng F, Zhu X, Park TG et al (2010) Co-delivery of siRNA and paclitaxel into cancer cells by biodegradable cationic micelles based on PDMAEMA–PCL–PDMAEMA triblock copolymers. Biomaterials 31:2408–2416
78. Zhang L, Radovic-Moreno AF, Alexis F, Gu FX, Basto PA, Bagalkot V et al (2007) Co-delivery of hydrophobic and hydrophilic drugs from nanoparticle–aptamer bioconjugates. Chem Med Chem 2:1268–1271
79. Mishra DK, Shandilya R, Mishra P (2018) Lipid based nanocarriers: a translational perspective. Nanomed Nanotechnol Biol Med 14(7):2023–2050
80. Prabhu RH, Patravale VB, Joshi MD (2015) Polymeric nanoparticles for targeted treatment in oncology: current insights. Int J Nanomed 10:1001
81. Kataoka K, Harada A, Nagasaki Y (2001) Block copolymer micelles for drug delivery: design, characterization and biological significance. Adv Drug Deliv Rev 47:113–131
82. Discher DE, Ortiz V, Srinivas G, Klein ML, Kim Y, Christian D et al (2007) Emerging applications of polymersomes in delivery: from molecular dynamics to shrinkage of tumors. Prog Polym Sci 32:838–857
83. Meng F, Zhong Z, Feijen J (2009) Stimuli-responsive polymersomes for programmed drug delivery. Biomacromol 10:197–209
84. Lee CC, MacKay JA, Fréchet JM, Szoka FC (2005) Designing dendrimers for biological applications. Nat Biotechnol 23:1517
85. Gao C, Yan D (2004) Hyperbranched polymers: from synthesis to applications. Prog Polym Sci 29:183–275
86. Bellomo EG, Wyrsta MD, Pakstis L, Pochan DJ, Deming TJ (2004) Stimuli-responsive polypeptide vesicles by conformation-specific assembly. Nat Mater 3:244
87. Peracchia M, Harnisch S, Pinto-Alphandary H, Gulik A, Dedieu J, Desmaele D et al (1999) Visualization of in vitro protein-rejecting properties of PEGylated stealth® polycyanoacrylate nanoparticles. Biomaterials 20:1269–1275
88. Gref R, Lück M, Quellec P, Marchand M, Dellacherie E, Harnisch S et al (2000) 'Stealth'corona-core nanoparticles surface modified by polyethylene glycol (PEG): influences of the corona (PEG chain length and surface density) and of the core composition on phagocytic uptake and plasma protein adsorption. Colloids Surf B 18:301–313
89. Wang M, Thanou M (2010) Targeting nanoparticles to cancer. Pharmacol Res 62:90–99
90. Vasey PA, Kaye SB, Morrison R, Twelves C, Wilson P, Duncan R et al (1999) Phase I clinical and pharmacokinetic study of PK1 [N-(2-hydroxypropyl) methacrylamide copolymer doxorubicin]: first member of a new class of chemotherapeutic agents—drug-polymer conjugates. Clin Cancer Res 5:83–94
91. Singer JW (2005) Paclitaxel poliglumex (XYOTAX™, CT-2103): a macromolecular taxane. J Control Release 109:120–126
92. Mitra AK, Cholkar K, Mandal A (2017) Emerging nanotechnologies for diagnostics, drug delivery and medical devices. In: Cholkar K, Acharya G, Trinh HM, Singh G (eds) Therapeutic applications of polymeric materials. Elsevier, New York, pp 1–19
93. Li C (2002) Poly (L-glutamic acid)–anticancer drug conjugates. Adv Drug Deliv Rev 54:695–713
94. Matsumura Y (2008) Poly (amino acid) micelle nanocarriers in preclinical and clinical studies. Adv Drug Deliv Rev 60:899–914
95. Lee KS, Chung HC, Im SA, Park YH, Kim CS, Kim S-B et al (2008) Multicenter phase II trial of Genexol-PM, a Cremophor-free, polymeric micelle formulation of paclitaxel, in patients with metastatic breast cancer. Breast Cancer Res Treat 108:241–250
96. Wiradharma NZY, Venkataraman S, Hedrick JL, Yang YY (2009) Self-assembled polymer nanostructures for delivery of anticancer therapeutics. Nano Today 4:302–317
97. Ke X-Y, Ng VWL, Gao S-J, Tong YW, Hedrick JL, Yang YY (2014) Co-delivery of thioridazine and doxorubicin using polymeric micelles for targeting both cancer cells and cancer stem cells. Biomaterials 35:1096–1108
98. Kim SC, Kim DW, Shim YH, Bang JS, Oh HS, Kim SW et al (2001) In vivo evaluation of polymeric micellar paclitaxel formulation: toxicity and efficacy. J Control Release 72:191–202
99. Kim D-W, Kim S-Y, Kim H-K, Kim S-W, Shin S, Kim J et al (2007) Multicenter phase II trial of Genexol-PM, a novel Cremophor-free, polymeric micelle formulation of paclitaxel, with cisplatin in patients with advanced non-small-cell lung cancer. Ann Oncol 18:2009–2014
100. Palmerston Mendes L, Pan J, Torchilin VP (2017) Dendrimers as nanocarriers for nucleic acid and drug delivery in cancer therapy. Molecules 22:1401
101. Zhong Q, Bielski ER, Rodrigues LS, Brown MR, Reineke JJ, da Rocha SR (2016) Conjugation to poly (amidoamine) dendrimers and pulmonary delivery reduce cardiac accumulation and enhance antitumor activity of doxorubicin in lung metastasis. Mol Pharm 13:2363–2375
102. Quintana A, Raczka E, Piehler L, Lee I, Myc A, Majoros I et al (2002) Design and function of a dendrimer-based therapeutic nanodevice targeted to tumor cells through the folate receptor. Pharm Res 19:1310–1316
103. Lohcharoenkal W, Wang L, Chen YC, Rojanasakul Y (2014) Protein nanoparticles as drug delivery carriers for cancer therapy. BioMed Res Int. https://doi.org/10.1155/2014/180549
104. Tarhini M, Greige-Gerges H, Elaissari A (2017) Protein-based nanoparticles: from preparation to encapsulation of active molecules. Int J Pharm 522:172–197
105. Nyman DW, Campbell KJ, Hersh E, Long K, Richardson K, Trieu V et al (2005) Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. J Clin Oncol 23:7785–7793
106. Desai N, Trieu V, Yao Z, Louie L, Ci S, Yang A et al (2006) Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. Clin Cancer Res 12:1317–1324
107. Srinivas G, Discher DE, Klein ML (2004) Self-assembly and properties of diblock copolymers by coarse-grain molecular dynamics. Nat Mater 3:638
108. Ahmed F, Pakunlu RI, Srinivas G, Brannan A, Bates F, Klein ML et al (2006) Shrinkage of a rapidly growing tumor by drug-loaded polymersomes: pH-triggered release through copolymer degradation. Mol Pharm 3:340–350
109. Hou B, Zheng B, Yang W, Dong C, Wang H, Chang J (2017) Construction of near infrared light triggered nanodumbbell for cancer photodynamic therapy. J Colloid Interface Sci 494:363–372
110. Xin Y, Yin M, Zhao L, Meng F, Luo L (2017) Recent progress on nanoparticle-based drug delivery systems for cancer therapy. Cancer Biol Med 14:228
111. Bayda S, Hadla M, Palazzolo S, Corona G, Toffoli G, Rizzolio F (2017) Inorganic nanoparticles for cancer therapy: a transition from lab to clinic. Curr Med Chem. https://doi.org/10.2174/0929867325666171229141156
112. Abbasi E, Kafshdooz T, Bakhtiary M, Nikzamir N, Nikzamir N, Nikzamir M et al (2016) Biomedical and biological applications of quantum dots. Artif Cell Nanomed Biotechnol 44:885–891
113. Chattopadhyay S, Dash SK, Mandal D, Das B, Tripathy S, Dey A et al (2016) Metal based nanoparticles as cancer antigen delivery vehicles for macrophage based antitumor vaccine. Vaccine 34:957–967

114. Chattopadhyay S, Dash SK, Tripathy S, Pramanik P, Roy S (2015) Phosphonomethyl iminodiacetic acid-conjugated cobalt oxide nanoparticles liberate Co++ ion-induced stress associated activation of TNF-α/p38 MAPK/caspase 8-caspase 3 signaling in human leukemia cells. J Biol Inorg Chem 20:123–141
115. Chattopadhyay S, Dash SK, Mahapatra SK, Tripathy S, Ghosh T, Das B et al (2014) Chitosan-modified cobalt oxide nanoparticles stimulate TNF-α-mediated apoptosis in human leukemic cells. J Biol Inorg Chem 19:399–414
116. Farrer NJ, Salassa L, Sadler PJ (2009) Photoactivated chemotherapy (PACT): the potential of excited-state d-block metals in medicine. Dalton Trans 48:10690–10701
117. Hernandez-Delgadillo R, Velasco-Arias D, Diaz D, Arevalo-Niño K, Garza-Enriquez M, De la Garza-Ramos MA et al (2012) Zerovalent bismuth nanoparticles inhibit Streptococcus mutans growth and formation of biofilm. Int J Nanomed 7:2109
118. Zhao P, Li N, Astruc D (2013) State of the art in gold nanoparticle synthesis. Coord Chem Rev 257:638–665
119. Her S, Jaffray DA, Allen C (2017) Gold nanoparticles for applications in cancer radiotherapy: mechanisms and recent advancements. Adv Drug Deliv Rev 109:84–101
120. Spyratou E, Makropoulou M, Efstathopoulos EP, Georgakilas AG, Sihver L (2017) Recent advances in cancer therapy based on dual mode gold nanoparticles. Cancers 9:173
121. Abadeer NS, Murphy CJ (2016) Recent progress in cancer thermal therapy using gold nanoparticles. J Phy Chem C 120:4691–4716
122. Bagheri S, Yasemi M, Safaie-Qamsari E, Rashidiani J, Abkar M, Hassani M et al (2018) Using gold nanoparticles in diagnosis and treatment of melanoma cancer. Artif Cells Blood Substit Biotechnol. https://doi.org/10.1080/21691401.2018.1430585
123. Huang X, O'Connor R, Kwizera EA (2017) Gold nanoparticle based platforms for circulating cancer marker detection. Nanotheranostics 1:80–102 **(Sydney, NSW)**
124. Barai AC, Paul K, Dey A, Manna S, Roy S, Bag BG et al (2018) Green synthesis of Nerium oleander-conjugated gold nanoparticles and study of its in vitro anticancer activity on MCF-7 cell lines and catalytic activity. Nano Converg 5:10
125. Ghosh P, Han G, De M, Kim CK, Rotello VM (2008) Gold nanoparticles in delivery applications. Adv Drug Deliv Rev 60:1307–1315
126. Rana S, Bajaj A, Mout R, Rotello VM (2012) Monolayer coated gold nanoparticles for delivery applications. Adv Drug Deliv Rev 64:200–216
127. Mieszawska AJ, Mulder WJ, Fayad ZA, Cormode DP (2013) Multifunctional gold nanoparticles for diagnosis and therapy of disease. Mol Pharm 10:831–847
128. Mi Y, Shao Z, Vang J, Kaidar-Person O, Wang AZ (2016) Application of nanotechnology to cancer radiotherapy. Cancer Nanotechnol 7:11
129. Schuemann J, Berbeco R, Chithrani DB, Cho SH, Kumar R, McMahon SJ et al (2016) Roadmap to clinical use of gold nanoparticles for radiation sensitization. International Journal of Radiation Oncology• Biology•. Physics 94:189–205
130. Patra CR, Bhattacharya R, Mukhopadhyay D, Mukherjee P (2010) Fabrication of gold nanoparticles for targeted therapy in pancreatic cancer. Adv Drug Deliv Rev 62:346–361
131. Patra CR, Bhattacharya R, Wang E, Katarya A, Lau JS, Dutta S et al (2008) Targeted delivery of gemcitabine to pancreatic adenocarcinoma using cetuximab as a targeting agent. Cancer Res 68:1970–1978
132. Jiang W, Kim BY, Rutka JT, Chan WC (2008) Nanoparticle-mediated cellular response is size-dependent. Nat Nanotechnol 3:145
133. Hirsch LR, Stafford RJ, Bankson J, Sershen SR, Rivera B, Price R et al (2003) Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. Proc Natl Acad Sci 100:13549–13554
134. Stern JM, Stanfield J, Lotan Y, Park S, Hsieh J-T, Cadeddu JA (2007) Efficacy of laser-activated gold nanoshells in ablating prostate cancer cells in vitro. J Endourol 21:939–943
135. Jain KK (2003) Nanodiagnostics: application of nanotechnology in molecular diagnostics. Expert Rev Mol Diagn 3:153–161
136. Bernstein AL, Dhanantwari A, Jurcova M, Cheheltani R, Naha PC, Ivanc T et al (2016) Improved sensitivity of computed tomography towards iodine and gold nanoparticle contrast agents via iterative reconstruction methods. Sci Rep 6:26177
137. Liao S, Chan CK, Ramakrishna S (2008) Stem cells and biomimetic materials strategies for tissue engineering. Mater Sci Eng C 28:1189–1202
138. Chung BGKL, Khademhosseini A (2007) Micro- and nanoscale technologies for tissue engineering and drug discovery applications. Expert Opin Drug Discov 2:1653–1668
139. Dvir T, Timko BP, Kohane DS, Langer R (2011) Nanotechnological strategies for engineering complex tissues. Nat Nanotechnol 6:13
140. Quaglia F (2008) Bioinspired tissue engineering: the great promise of protein delivery technologies. Int J Pharm 364:281–297
141. Santo VE, Duarte ARC, Popa EG, Gomes ME, Mano JF, Reis RL (2012) Enhancement of osteogenic differentiation of human adipose derived stem cells by the controlled release of platelet lysates from hybrid scaffolds produced by supercritical fluid foaming. J Control Release 162:19–27
142. Santo VE, Gomes ME, Mano JF, Reis RL (2013) Controlled release strategies for bone, cartilage, and osteochondral engineering—part I: recapitulation of native tissue healing and variables for the design of delivery systems. Tissue Eng B Rev 19:308–326
143. Xing Z-C, Han S-J, Shin Y-S, Kang I-K (2011) Fabrication of biodegradable polyester nanocomposites by electrospinning for tissue engineering. J Nanomater. https://doi.org/10.1155/2011/929378
144. Li C, Vepari C, Jin H-J, Kim HJ, Kaplan DL (2006) Electrospun silk-BMP-2 scaffolds for bone tissue engineering. Biomaterials 27:3115–3124
145. Silva G, Pedro A, Costa F, Neves N, Coutinho O, Reis R (2005) Soluble starch and composite starch bioactive glass 45S5 particles: synthesis, bioactivity, and interaction with rat bone marrow cells. Mater Sci Eng C 25:237–246
146. Habraken W, Wolke J, Jansen J (2007) Ceramic composites as matrices and scaffolds for drug delivery in tissue engineering. Adv Drug Deliv Rev 59:234–248
147. Luz GM, Mano JF (2012) Chitosan/bioactive glass nanoparticles composites for biomedical applications. Biomed Mater 7:054104
148. Martins A, Reis RL, Neves NM (2013) Electrospinning: processing technique for tissue engineering scaffolding. J Int Mater Rev 53:257–274
149. Poste GKR (1983) Site–specific (targeted) drug delivery in cancer therapy. Nat Biotechnol 1:869–878
150. Yu X, Trase I, Ren M, Duval K, Guo X, Chen Z (2016) Design of nanoparticle-based carriers for targeted drug delivery. J Nanomater. https://doi.org/10.1155/2016/1087250
151. Rabanel M (2012) J, Aoun V, Elkin I, Mokhtar M, Hildgen P. Drug-loaded nanocarriers: passive targeting and crossing of biological barriers. Curr Med Chem 19:3070–3102
152. Mercado AE, Ma J, He X, Jabbari E (2009) Release characteristics and osteogenic activity of recombinant human bone morphogenetic protein-2 grafted to novel self-assembled poly (lactide-co-glycolide fumarate) nanoparticles. J Control Release 140:148–156
153. Chen L, Liu L, Li C, Tan Y, Zhang G (2011) A new growth factor controlled drug release system to promote healing of bone

fractures: nanospheres of recombinant human bone morphogenetic-2 and polylactic acid. J Nanosci Nanotechnol 11:3107–3114
154. Oliveira JM, Sousa RA, Kotobuki N, Tadokoro M, Hirose M, Mano JF et al (2009) The osteogenic differentiation of rat bone marrow stromal cells cultured with dexamethasone-loaded carboxymethylchitosan/poly (amidoamine) dendrimer nanoparticles. Biomaterials 30:804–813
155. Shah DA, Kwon S-J, Bale SS, Banerjee A, Dordick JS, Kane RS (2011) Regulation of stem cell signaling by nanoparticle-mediated intracellular protein delivery. Biomaterials 32:3210–3219
156. Fanord F, Fairbairn K, Kim H, Garces A, Bhethanabotla V, Gupta VK (2010) Bisphosphonate-modified gold nanoparticles: a useful vehicle to study the treatment of osteonecrosis of the femoral head. Nanotechnology 22:035102
157. Jensen T, Baas J, Dolathshahi-Pirouz A, Jacobsen T, Singh G, Nygaard JV et al (2011) Osteopontin functionalization of hydroxyapatite nanoparticles in a PDLLA matrix promotes bone formation. J Biomed Mater Res A 99:94–101
158. Walmsley GG, McArdle A, Tevlin R, Momeni A, Atashroo D, Hu MS et al (2015) Nanotechnology in bone tissue engineering. Nanomed Nanotechnol Biol Med 11:1253–1263
159. Chou LY, Ming K, Chan WC (2011) Strategies for the intracellular delivery of nanoparticles. Chem Soc Rev 40:233–245
160. Albanese A, Tang PS, Chan WC (2012) The effect of nanoparticle size, shape, and surface chemistry on biological systems. Annu Rev Biomed Eng 14:1–16
161. Li Y, Kröger M, Liu WK (2015) Shape effect in cellular uptake of PEGylated nanoparticles: comparison between sphere, rod, cube and disk. Nanoscale 7:16631–16646
162. Saha RN, Vasanthakumar S, Bende G, Snehalatha M (2010) Nanoparticulate drug delivery systems for cancer chemotherapy. Mol Membr Biol 27:215–231
163. Sahu A, Choi WI, Lee JH, Tae G (2013) Graphene oxide mediated delivery of methylene blue for combined photodynamic and photothermal therapy. Biomaterials 34:6239–6248
164. Wang Y, Wang K, Zhao J, Liu X, Bu J, Yan X et al (2013) Multifunctional mesoporous silica-coated graphene nanosheet used for chemo-photothermal synergistic targeted therapy of glioma. J Am Chem Soc 135:4799–4804
165. Kansara K, Patel P, Shukla RK, Pandya A, Shanker R, Kumar A et al (2018) Synthesis of biocompatible iron oxide nanoparticles as a drug delivery vehicle. Int J Nanomed 13:79
166. McBain SC, Yiu HH, Dobson J (2008) Magnetic nanoparticles for gene and drug delivery. Int J Nanomed 3:169
167. Schleich N, Po C, Jacobs D, Ucakar B, Gallez B, Danhier F et al (2014) Comparison of active, passive and magnetic targeting to tumors of multifunctional paclitaxel/SPIO-loaded nanoparticles for tumor imaging and therapy. J Control Release 194:82–91
168. Zare T, Sattarahmady N (2016) A mini-review of magnetic nanoparticles: applications in biomedicine. Basic Clin Cancer Res 7:29–39
169. Holzinger M, Le Goff A, Cosnier S (2014) Nanomaterials for biosensing applications: a review. Front Chem 2:63
170. Holzinger M, Le Goff A, Cosnier S (2017) Synergetic effects of combined nanomaterials for biosensing applications. Sensors 17:1010
171. Su J, Goldberg AF, Stoltz BM (2016) Label-free detection of single nanoparticles and biological molecules using microtoroid optical resonators. Light Sci Appl 5:e16001
172. Lu K, Aung T, Guo N, Weichselbaum R, Lin W (2018) Nanoscale metal–organic frameworks for therapeutic, imaging, and sensing applications. Adv Mater. https://doi.org/10.1002/adma.201707634
173. He C, Lu K, Lin W (2014) Nanoscale metal–organic frameworks for real-time intracellular pH sensing in live cells. J Am Chem Soc 136:12253–12256
174. Xu R, Wang Y, Duan X, Lu K, Micheroni D, Hu A et al (2016) Nanoscale metal–organic frameworks for ratiometric oxygen sensing in live cells. J Am Chem Soc 138:2158–2161
175. Wu P, Wang J, He C, Zhang X, Wang Y, Liu T et al (2012) Luminescent metal-organic frameworks for selectively sensing nitric oxide in an aqueous solution and in living cells. Adv Funct Mater 22:1698–1703
176. Stohs SJ, Bagchi D (1995) Oxidative mechanisms in the toxicity of metal ions. Free Radical Biol Med 18:321–336
177. Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ramírez JT et al (2005) The bactericidal effect of silver nanoparticles. Nanotechnology 16:2346
178. Yamanaka M, Hara K, Kudo J (2005) Bactericidal actions of a silver ion solution on *Escherichia coli*, studied by energy-filtering transmission electron microscopy and proteomic analysis. Appl Environ Microbiol 71:7589–7593
179. Sarkar S, Jana AD, Samanta SK, Mostafa G (2007) Facile synthesis of silver nano particles with highly efficient anti-microbial property. Polyhedron 26:4419–4426
180. Shrivastava S, Bera T, Roy A, Singh G, Ramachandrarao P, Dash D (2007) Characterization of enhanced antibacterial effects of novel silver nanoparticles. Nanotechnology 18:225103
181. Shahverdi AR, Fakhimi A, Shahverdi HR, Minaian S (2007) Synthesis and effect of silver nanoparticles on the antibacterial activity of different antibiotics against *Staphylococcus aureus* and *Escherichia coli*. Nanomed Nanotechnol Biol Med 3:168–171
182. Swamy MK, Sudipta K, Jayanta K, Balasubramanya S (2015) The green synthesis, characterization, and evaluation of the biological activities of silver nanoparticles synthesized from Leptadenia reticulata leaf extract. Appl Nanosci 5:73–81
183. Swamy MK, Akhtar MS, Mohanty SK, Sinniah UR (2015) Synthesis and characterization of silver nanoparticles using fruit extract of *Momordica cymbalaria* and assessment of their in vitro antimicrobial, antioxidant and cytotoxicity activities. Spectrochim Acta Part A Mol Biomol Spectrosc 151:939–944
184. Akhtar M, Swamy MK, Umar A, Sahli A, Abdullah A (2015) Biosynthesis and characterization of silver nanoparticles from methanol leaf extract of *Cassia didymobotrya* and assessment of their antioxidant and antibacterial activities. J Nanosci Nanotechnol 15:9818–9823
185. Mandal D, Dash SK, Das B, Chattopadhyay S, Ghosh T, Das D et al (2016) Bio-fabricated silver nanoparticles preferentially targets Gram positive depending on cell surface charge. Biomed Pharmacother 83:548–558
186. Das B, Dash SK, Mandal D, Ghosh T, Chattopadhyay S, Tripathy S et al (2017) Green synthesized silver nanoparticles destroy multidrug resistant bacteria via reactive oxygen species mediated membrane damage. Arab J Chem 10:862–876
187. Yamamoto O, Sawai J, Sasamoto T (2000) Change in antibacterial characteristics with doping amount of ZnO in MgO–ZnO solid solution. Int J Inorg Mater 2:451–454
188. Sawai J, Shiga H, Kojima H (2001) Kinetic analysis of death of bacteria in CaO powder slurry. Int Biodeterior Biodegradation 47:23–26
189. Tang Z-X, Lv B-F (2014) MgO nanoparticles as antibacterial agent: preparation and activity. Braz J Chem Eng 31:591–601
190. Sawai J, Kojima H, Igarashi H, Hashimoto A, Shoji S, Sawaki T et al (2000) Antibacterial characteristics of magnesium oxide powder. World J Microbiol Biotechnol 16:187–194
191. Richards R, Li W, Decker S, Davidson C, Koper O, Zaikovski V et al (2000) Consolidation of metal oxide nanocrystals. Reactive pellets with controllable pore structure that represent a new family of porous, inorganic materials. J Am Chem Soc 122:4921–4925
192. Koper OB, Klabunde JS, Marchin GL, Klabunde KJ, Stoimenov P, Bohra L (2002) Nanoscale powders and formulations with

biocidal activity toward spores and vegetative cells of bacillus species, viruses, and toxins. Curr Microbiol 44:49–55
193. Krishnamoorthy K, Manivannan G, Kim SJ, Jeyasubramanian K, Premanathan M (2012) Antibacterial activity of MgO nanoparticles based on lipid peroxidation by oxygen vacancy. J Nanopart Res 14:1063
194. Linsebigler AL, Lu G, Yates JT Jr (1995) Photocatalysis on TiO2 surfaces: principles, mechanisms, and selected results. Chem Rev 95:735–758
195. Hirakawa K, Mori M, Yoshida M, Oikawa S, Kawanishi S (2004) Photo-irradiated titanium dioxide catalyzes site specific DNA damage via generation of hydrogen peroxide. Free Radical Res 38:439–447
196. Wong M-S, Chu W-C, Sun D-S, Huang H-S, Chen J-H, Tsai P-J et al (2006) Visible-light-induced bactericidal activity of a nitrogen-doped titanium photocatalyst against human pathogens. Appl Environ Microbiol 72:6111–6116
197. Besinis A, De Peralta T, Handy RD (2014) The antibacterial effects of silver, titanium dioxide and silica dioxide nanoparticles compared to the dental disinfectant chlorhexidine on Streptococcus mutans using a suite of bioassays. Nanotoxicology 8:1–16
198. Yamamoto O (2001) Influence of particle size on the antibacterial activity of zinc oxide. Int J Inorg Mater 3:643–646
199. Padmavathy N, Vijayaraghavan R (2008) Enhanced bioactivity of ZnO nanoparticles—an antimicrobial study. Sci Technol Adv Mater 9:035004
200. Jones N, Ray B, Ranjit KT, Manna AC (2008) Antibacterial activity of ZnO nanoparticle suspensions on a broad spectrum of microorganisms. FEMS Microbiol Lett 279:71–76
201. Liu Y, He L, Mustapha A, Li H, Hu Z, Lin M (2009) Antibacterial activities of zinc oxide nanoparticles against Escherichia coli O157: h7. J Appl Microbiol 107:1193–1201
202. Gil-Tomás J, Tubby S, Parkin IP, Narband N, Dekker L, Nair SP et al (2007) Lethal photosensitisation of Staphylococcus aureus using a toluidine blue O–tiopronin–gold nanoparticle conjugate. J Mater Chem 17:3739–3746
203. Kuo W-S, Chang C-N, Chang Y-T, Yeh C-S (2009) Antimicrobial gold nanorods with dual-modality photodynamic inactivation and hyperthermia. Chem Commun. https://doi.org/10.1039/B907274H
204. Pissuwan D, Cortie CH, Valenzuela SM, Cortie MB (2010) Functionalised gold nanoparticles for controlling pathogenic bacteria. Trends Biotechnol 28:207–213
205. Perni S, Piccirillo C, Pratten J, Prokopovich P, Chrzanowski W, Parkin IP et al (2009) The antimicrobial properties of light-activated polymers containing methylene blue and gold nanoparticles. Biomaterials 30:89–93
206. Zharov VP, Mercer KE, Galitovskaya EN, Smeltzer MS (2006) Photothermal nanotherapeutics and nanodiagnostics for selective killing of bacteria targeted with gold nanoparticles. Biophys J 90:619–627
207. Bapista PPE, Eaton P, Doria G, Miranda A, Gomes I, Quaresma P, Franco R (2008) Gold nanoparticles for the development of clinical diagnosis methods. Anal Bioanal Chem 391:943–950
208. Gu H, Ho P, Tong E, Wang L, Xu B (2003) Presenting vancomycin on nanoparticles to enhance antimicrobial activities. Nano Lett 3:1261–1263
209. Burygin G, Khlebtsov B, Shantrokha A, Dykman L, Bogatyrev V, Khlebtsov N (2009) On the enhanced antibacterial activity of antibiotics mixed with gold nanoparticles. Nanoscale Res Lett 4:794
210. Grace AN, Pandian K (2007) Antibacterial efficacy of aminoglycosidic antibiotics protected gold nanoparticles—a brief study. Colloids Surf A Physicochemical Eng Asp 297:63–70
211. Saha B, Bhattacharya J, Mukherjee A, Ghosh A, Santra C, Dasgupta AK et al (2007) In vitro structural and functional evaluation of gold nanoparticles conjugated antibiotics. Nanoscale Res Lett 2:614
212. Rai A, Prabhune A, Perry CC (2010) Antibiotic mediated synthesis of gold nanoparticles with potent antimicrobial activity and their application in antimicrobial coatings. J Mater Chem 20:6789–6798
213. Chatterjee AK, Sarkar RK, Chattopadhyay AP, Aich P, Chakraborty R, Basu T (2012) A simple robust method for synthesis of metallic copper nanoparticles of high antibacterial potency against E. coli. Nanotechnology 23:085103
214. Sampath M, Vijayan R, Tamilarasu E, Tamilselvan A, Sengottuvelan B (2014) Green synthesis of novel jasmine bud-shaped copper nanoparticles. J Nanotechnol. https://doi.org/10.1155/2014/626523
215. Raffi M, Mehrwan S, Bhatti TM, Akhter JI, Hameed A, Yawar W et al (2010) Investigations into the antibacterial behavior of copper nanoparticles against *Escherichia coli*. Ann Microbiol 60:75–80
216. Ruparelia JP, Chatterjee AK, Duttagupta SP, Mukherji S (2008) Strain specificity in antimicrobial activity of silver and copper nanoparticles. Acta Biomater 4:707–716
217. Mohammad G, Mishra VK, Pandey H (2008) Antioxidant properties of some nanoparticle may enhance wound healing in T2DM patient. Digest J Nanomater Biostruct 3:159–162
218. Hernandez-Delgadillo R, Velasco-Arias D, Martinez-Sanmiguel JJ, Diaz D, Zumeta-Dube I, Arevalo-Niño K et al (2013) Bismuth oxide aqueous colloidal nanoparticles inhibit Candida albicans growth and biofilm formation. Int J Nanomed 8:1645
219. Luo Y, Hossain M, Wang C, Qiao Y, An J, Ma L et al (2013) Targeted nanoparticles for enhanced X-ray radiation killing of multidrug-resistant bacteria. Nanoscale 5:687–694
220. Nazari P, Dowlatabadi-Bazaz R, Mofid M, Pourmand M, Daryani N, Faramarzi M et al (2014) The antimicrobial effects and metabolomic footprinting of carboxyl-capped bismuth nanoparticles against *Helicobacter pylori*. Appl Biochem Biotechnol 172:570–579
221. Leid JG, Ditto AJ, Knapp A, Shah PN, Wright BD, Blust R et al (2011) In vitro antimicrobial studies of silver carbene complexes: activity of free and nanoparticle carbene formulations against clinical isolates of pathogenic bacteria. J Antimicrob Chemother 67:138–148
222. Arias LR, Yang L (2009) Inactivation of bacterial pathogens by carbon nanotubes in suspensions. Langmuir 25:3003–3012
223. Dong L, Henderson A, Field C (2012) Antimicrobial activity of single-walled carbon nanotubes suspended in different surfactants. J Nanotechnol. https://doi.org/10.1155/2012/928924
224. Tegos GP, Demidova TN, Arcila-Lopez D, Lee H, Wharton T, Gali H et al (2005) Cationic fullerenes are effective and selective antimicrobial photosensitizers. Chem Biol 12:1127–1135
225. Cataldo F, Da Ros T (2008) Medicinal chemistry and pharmacological potential of fullerenes and carbon nanotubes. Springer Science & Business Media, Berlin
226. Nakamura S, Mashino T (2009) Biological activities of water-soluble fullerene derivatives. Journal of Physics: Conference Series: IOP Publishing p. 012003
227. Akhavan O, Ghaderi E (2010) Toxicity of graphene and graphene oxide nanowalls against bacteria. ACS Nano 4:5731–5736
228. Zhou C, Qi X, Li P, Chen WN, Mouad L, Chang MW et al (2009) High potency and broad-spectrum antimicrobial peptides synthesized via ring-opening polymerization of α-aminoacid-N-carboxyanhydrides. Biomacromol 11:60–67
229. Beyth N, Houri-Haddad Y, Domb A, Khan W, Hazan R (2015) Alternative antimicrobial approach: nano-antimicrobial materials. Evid Based Complement Alternat Med. https://doi.org/10.1155/2015/246012

230. Sauvet G, Fortuniak W, Kazmierski K, Chojnowski J (2003) Amphiphilic block and statistical siloxane copolymers with antimicrobial activity. J Polym Sci Part A Polym Chem 41:2939–2948
231. Zhang H, Wang D, Butler R, Campbell NL, Long J, Tan B et al (2008) Formation and enhanced biocidal activity of water-dispersable organic nanoparticles. Nat Nanotechnol 3:506
232. Lara HH, Ayala-Nuñez NV, Ixtepan-Turrent L, Rodriguez-Padilla C (2010) Mode of antiviral action of silver nanoparticles against HIV-1. J Nanobiotechnol 8:1
233. Antoine TE, Hadigal SR, Yakoub AM, Mishra YK, Bhattacharya P, Haddad C et al (2016) Intravaginal zinc oxide tetrapod nanoparticles as novel immunoprotective agents against genital herpes. J Immunol 196:4566–4575
234. Broglie JJ, Alston B, Yang C, Ma L, Adcock AF, Chen W et al (2015) Antiviral activity of gold/copper sulfide core/shell nanoparticles against human norovirus virus-like particles. PLoS One 10:e0141050
235. Amirkhanov RNMN, Amirkhanov NV (2015) Zarytova VF Composites of peptide nucleic acids with titanium dioxide nanoparticles IV Antiviral activity of nanocomposites containing DNA/PNA duplexes. Russ J Bioorg Chem 41:140–146
236. de Silva JMSE, Santos MI, Kobarg J, Bajgelman MC, Cardoso MB (2016) Viral inhibition mechanism mediated by surface-modified silica nanoparticles. ACS Appl Mater Interfaces 8:16564–16572
237. Lin Z, Li Y, Guo M, Xu T, Wang C, Zhao M et al (2017) The inhibition of H1N1 influenza virus-induced apoptosis by silver nanoparticles functionalized with zanamivir. RSC Adv 7:742–750
238. Gaikwad S, Ingle A, Gade A, Rai M, Falanga A, Incoronato N et al (2013) Antiviral activity of mycosynthesized silver nanoparticles against herpes simplex virus and human parainfluenza virus type 3. Int J Nanomed 8:4303
239. Tutaj K, Szlazak R, Szalapata K, Starzyk J, Luchowski R, Grudzinski W et al (2016) Amphotericin B-silver hybrid nanoparticles: synthesis, properties and antifungal activity. Nanomed Nanotechnol Biol Med 12:1095–1103
240. Chudzik B, Czernel G, Miaskowski A, Gagoś M (2017) Amphotericin B-copper (II) complex shows improved therapeutic index in vitro. Eur J Pharm Sci 97:9–21
241. Viet PV, Nguyen HT, Cao TM, Hieu LV (2016) Fusarium antifungal activities of copper nanoparticles synthesized by a chemical reduction method. J Nanomater 2016:6
242. Ingale AG, Chaudhari AN (2013) Biogenic synthesis of nanoparticles and potential applications: an eco-friendly approach. J Nanomed Nanotechol 4:165
243. Samberg ME, Oldenburg SJ, Monteiro-Riviere NA (2010) Evaluation of silver nanoparticle toxicity in skin in vivo and keratinocytes in vitro. Environ Health Perspect 118:407
244. Zhang J, Wu L, Chan H-K, Watanabe W (2011) Formation, characterization, and fate of inhaled drug nanoparticles. Adv Drug Deliv Rev 63:441–455
245. Wu L, Zhang J, Watanabe W (2011) Physical and chemical stability of drug nanoparticles. Adv Drug Deliv Rev 63:456–469
246. Dreaden EC, Alkilany AM, Huang X, Murphy CJ, El-Sayed MA (2012) The golden age: gold nanoparticles for biomedicine. Chem Soc Rev 41:2740–2779