Recent Trends of Nano-material as Antimicrobial Agents

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Abstract Nanomaterial has been employed as an alternative to antibiotics, diagnostic tools and delivery of therapeutics. In particular, nanomaterial has grabbed the attention of researchers due to their antimicrobial properties due to the emergence of multi-drug resistance of several micro-organisms. The present chapter highlights the antimicrobial nanomaterials with their mechanism of action along with their broad spectrum applications such as silver nanomaterial is antimicrobial in nature and is effective in drug delivery. Metallic, non-metallic and natural/ biodegradable

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nanomaterials have been discussed as potential antimicrobial and their mode of action. The mechanism of antimicrobial nanomaterial is poorly understood, but oxidative stress, non-oxidative action, inhibition of cell adhesion, decline in biofilm formation, obstructed quoram sensing and metal ion release are attributed to be as the major reasons. In addition, the limitation and toxicity with the clinical and environmental applications are also described.

Keywords Nanomaterial · Antimicrobial · Drug resistance · Toxicity · Oxidative stress · Biofilm

1 Introduction

Since ages, microbial contamination is amongst the major factor for morbidity and mortality across the world. As per reports, in developing countries, almost half of the population is affected by microbial contaminants and causes more than three million people die annually (Armentano et al. 2014). Instead of, great advances in diagnostics and therapeutics; microbes continue to affect biomedical and healthcare sectors due to the development of antibiotic resistance (Schwartz et al. 1997). According to the WHO 2018 release on the high-level risk of antimicrobial resistance states that, worldwide across 22 countries, 500,000 individuals are suffering from antimicrobial resistance revealing the increasing risk of serious health alignments due to microbial infection (Organization 2018). For instance, in patients with antiretroviral treatment, the resistance of malaria for artemisinin is at its pace which increases the resistance of anti-human immunodeficiency virus (HIV) drug (Organization 2016). A number of contributing factors for such increase include the change in human lifestyle, industrialization, wars, and microbial genome mutations. These pathogens are not only responsible for the deterioration in healthcare but are also responsible for damaging crops, food spoilage, deterioration of textiles etc. Therefore, preservation of potency of existing antibiotics through a wiser use of their properties and developing better alternatives calls for an urgent quest.

Super-bacteria is resistant to almost all antibiotics due to their abuse. It has been shown that the resistance is because of gene called NDM (Hsueh 2010). The major three bacterial targets antibiotics are: cell wall synthesis, DNA replication mechanism, and translational mechanism. Antimicrobial mechanisms with nanomaterial against antibiotic-resistant microbes work by direct contact with the bacterial cell wall, without penetrating the cell, enhances release of antimicrobial metal ions from nanoparticle surfaces as shown in Fig. 1. This gives the hope that nanomaterial is considered less prone to promoting resistance. In the last few decades, nanostructure-based antimicrobial agents have drawn considerable attention to combat antimicrobial resistance. Nanomaterial holds unique characteristic features including electrical, optical, chemical and thermal. These unique properties provide application of nanomaterial in multidisciplinary fields of medicine, technology and industries (Refer Table 1). The basic properties of nanomaterial should be an inexpensive, effective and broad-spectrum effect.

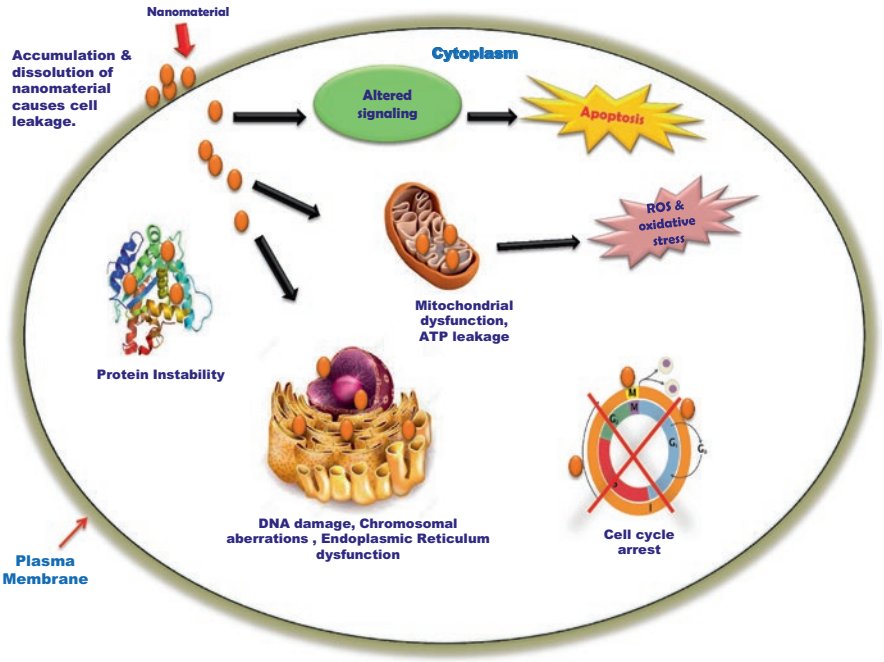

Fig. 1 Mechanism of nanomaterial against microbial cell: nanomaterial can cross the cell membrane barrier due to its accumulation, nano-size and shape. When nanomaterial enter the cytoplasm it can interfere with the cell organelles, proteins and signaling cascade as a result the cell could not survive due to apoptosis, cell cycle arrest, oxidative stress, protein instability, or damaged DNA

Table 1 Application and mechanism of nanomaterial

S.no.	Nanomaterial	Size (average)	Test micro-organism	Mechanism	Potential industrial application	References
1.	ZnO	12–60 nm	*E. coli, S. aureus*	Membrane disruption and ROS generation	Antimicrobial creams, lotions and ointments, sunscreen lotions, deodorants, ceramics, and self-cleaning glass	Gunalan et al. (2012)
2.	Ag	12–50 nm	*Pseudomonas aeruginosa, S. aureus, Candida albicans, E.coli, Vibrio cholerae, Salmonella typhi*	Membrane disruption, Ag ion interference with DNA replication,	Next generation antibiotics, medical, and health care products	Srisitthiratkul et al. (2011)

(continued)

Table 1 (continued)

S.no.	Nanomaterial	Size (average)	Test micro-organism	Mechanism	Potential industrial application	References
3.	Cu	100 nm	*E. coli, Bacillus subtilis, Candida albicans*	Protein inactivation via thiol interaction	Dental materials	Jadhav et al. (2011)
4.	Fe_3O_4	8–10 nm	*S. aureus, Staphylococcus epidermidis, Bacillus cereus*, *Klebsiellapneumonia*	Membrane disruption and ROS generation	Biomedical and antimicrobial applications	Ansari et al. (2017)
5.	Al_2O_3	11-60 nm	*E. coli, B. subtilis, Pseudomonas fluorescens*	Flocculation, dose dependent ROS and penetration of particle	Antibacterial applications	Jiang et al. (2009) and Simon-Deckers et al. (2009)
6.	TiO_2	17 nm	*E.coli, C. albicans*	Disruption of membrane	Next generation antibacterial and antifungal agent	Bahri-Laleh et al. (2011) and Simon-Deckers et al. (2009)
7.	SiO_2	20 nm	*E. coli, B. subtilis, P. fluorescens*	Disruption of membrane, flocculation	Biomedical and food applications	Jiang et al. (2009)
8.	Chitosan	40 nm	*E. coli, S. aureus, E. agglomerans*	Flocculation, membrane disruption	Biomedical devices, water filters, and instrument preparation	Kumar et al. (2017) and Qi et al. (2004)
9.	SWNT	0.83 nm and 5–50 nm	*E. coli, B. subtilis, P. aeruginosa, S. aureus*	Membrane disruption, interference with DNA replication	Medical devices, anti-biofouling membranes, and wastewater treatment	Liu et al. (2009)
10.	Dendrimers	NR	*P. aeruginosa, S. aureus,* strains of human cytomegavirus (HCMV), *C. albicans*	Kill biofilm cells, blocks virion attachment to target cells, membrane damage	Potential for drug delivery, anti-infective agents	Scorciapino et al. (2017)

2 Classification of Nanomaterial as Antimicrobial Agents

The increasing risk of antimicrobial resistance can be resolved with the help of upcoming approach to utilise the nanomaterial as antimicrobial. Nanomaterial possesses various physical, chemical and biological properties due to the nano-sized material. Different nano-material behaves differently against different microbes. Nanomaterial act by disrupting the bacterial membrane, hindering biofilm formation, acts as a carrier of antibiotics and acting against various mechanisms simultaneously. The nanomaterial causes antimicrobial action by either interacting directly with microorganisms or by oxidising the cell components or generates of reactive oxygen species which induces stress. Nanoparticles range from 1 to 100 nm in diameter. Depending upon composition and size, nanoparticles have unique properties in comparison to the bulk material. These are the surface area to volume ratio, surface Plasmon resonance, super-magnetization, surface-enhanced Raman scattering, photoluminescence, electric and heat conductivity and surface catalytic activity. As cell organelles and bio-molecules are in nano-size, nano-material can be combined with enzymes, antibodies, peptides, nucleic acids etc. Such modifications would provide specific functions to nanostructured material. Functionalization can be achieved by adsorption, linking with thiol groups, covalent bonding and electrostatic interactions (Sperling and Parak 2010). The nanomaterial used as antimicrobial can be classified on the basis of metallic, and non-metallic properties as mentioned in Fig. 2. Various reports focus on metals and metallic nanoparticles against micro-organisms (Chwalibog et al. 2010).

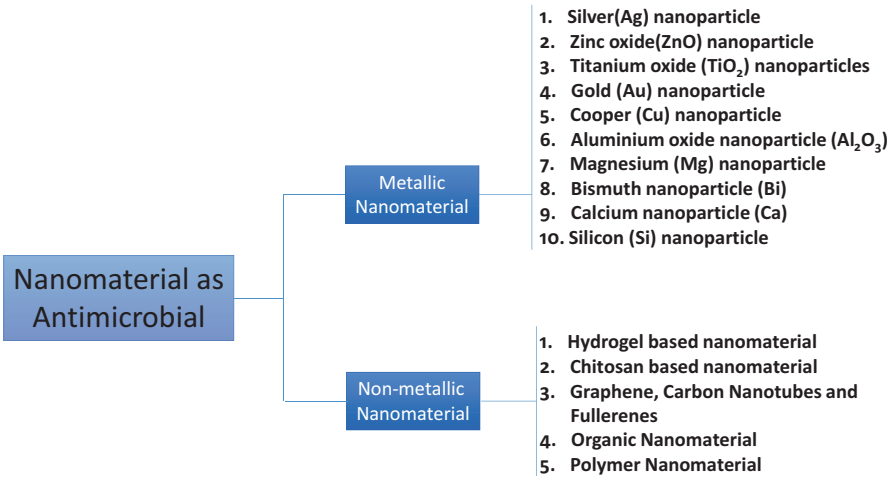

Fig. 2 Classification of nanomaterial as antimicrobial on the basic of metallic and non-metallic nature

2.1 Metallic Nanomaterial

Metals are potent antimicrobials and are vital for physiological activities in prokaryotic as well as eukaryotic cells such as iron acts as a cofactor for various enzymes, also essential for DNA replication, transcription and other metabolic processes (Andreini et al. 2008). Therefore, high levels of important metal ions are harmful to live organisms. Such nanostructured particles can be employed as they provide large surface area with increased reactivity. Several metal nanoparticles are known to possess antimicrobial properties such as Silver (Ag), Gold (Au), Copper (Cu), Zinc (Zn), Titanium (Ti), and Magnesium (Mg). Metal oxides have also been considered for their antimicrobial properties such as silver oxide (Ag_2O), titanium dioxide (TiO_2), silicon (Si), copper oxide (CuO), zinc oxide (ZnO), calcium oxide (CaO) and magnesium oxide (MgO). Metal oxide nanomaterial poses bactericidal due to the generation of reactive oxygen species (ROS), their physical structure and ion release (Fernando et al. 2018).

2.1.1 Silver (Ag) Nanoparticles

Silver salts and silver element are well known for their broad-spectrum antimicrobial properties. It has been used since ages to disinfect medical devices and for purification of water. It has been used as a pharmaceutical to recover from wounds, burns and other infections (Avalos et al. 2016). Therefore silver nanoparticle can act more efficiently as an antimicrobial agent. Ag nanoparticle is an antimicrobial which can act against gram positive and gram negative bacteria, as well as yeast (Luo et al. 2013). Ag nanoparticles possess various mechanisms for antimicrobial resistance. Ag+ interacts with sulphur and phosphorus groups of proteins present in the cell wall and cell membrane (Lara et al. 2010). Therefore, binds to negatively charged groups present resulting in holes in the membrane, leading to efflux of the cytoplasmic contents out of the cell along with the movement of H+ ions and this leads to cell death (Zhang et al. 2010). Nonetheless, Gram-positive bacteria are more susceptible than Gram-negative bacteria to the activity of Ag nanoparticles, as the ions get trapped in the lipopolysaccharide (LPS) of the Gram-negative bacteria which cannot penetrate in the cell (Lara et al. 2010). Within the microbial cell, Ag nanoparticles act by various mechanisms including inhibition of electron transport via cytochrome, binds to and damages DNA and RNA of the microorganism thereby, also inhibits DNA replication and cell cycle, prevents protein translocation by denaturing the 30S subunit of ribosomal, releases ROS which is toxic to the microbial cell (Huang et al. 2011). At nano-scale Ag possess antifungal, anti-bacterial and anti-viral properties. The antimicrobial properties of Ag contribute towards its wide application in medical devices, home appliance, some biosensors, etc.

Silver oxide (Ag_2O) nanoparticle was previously discovered, possessing the antimicrobial activity. These nanoparticles can be used as a substitute of antibiotics

to a greater extent. The efficacy of Ag_2O was previously demonstrated on the basis of the effect these nanoparticle cause on E.coli. The DNA of the microbes losses the ability to DNA replication and arrests the cell cycle by causing DNA damage (Allahverdiyev et al. 2011). Hence with further research and advancement of various compounds, alloys can be generated for a better application.

2.1.2 Zinc Oxide (ZnO) Nanoparticles

ZnO containing nanomaterial has a potential antimicrobial effect especially against gram-positive and gram-negative bacteria; therefore, zinc oxide nanocomposites are being used in packing food (Espitia et al. 2013). The mode of antimicrobial activity of ZnO is the release of Zn2+ and ROS generation which damages the lipids and proteins of the cell membrane as well as that present inside the cell and interacts with essential metabolic pathways leading to cell death (Chupani et al. 2017). ZnO nanomaterial when coated with polyvinyl alcohol (PVA) increases the permeability of the membrane, easily enters into the cytoplasm and creates oxidative stress (Hajipour et al. 2012). ZnO nanomaterial, when combined with polymethylmethacrylate (PMMA), inhibits fungal biofilm formation that can treat denture stomatitis. Studies also suggest that ZnO also induces the production of p53 tumour suppressor protein that leads to apoptosis of cancer cells in human (Akhtar et al. 2012).

2.1.3 Titanium Oxide (TiO_2) Nanoparticles

The antimicrobial activity of TiO_2 is due to its structure as crystal and its specific size and shape. Titanium oxide (TiO_2) alone or conjugation with other antimicrobial agent is non-toxic and have antimicrobial activity. TiO_2 nanomaterial is used in varied products such as lotions, toothpaste, paints, coatings etc. due to whiteness properties and high refractive index. Due to its antimicrobial properties, it is used as a disinfectant in potable water.TiO_2 nanoparticles contain specific photocatalytic properties due to which it can act more effectively as an antimicrobial. This photocatalytic activity helps TiO_2 nanoparticles to generate ROS under UV-light. The mode of action of TiO_2 nanomaterial is by ROS generation especially –OH free radicals (Dizaj et al. 2014).

2.1.4 Gold (Au) Nanoparticles

Gold nanomaterial is a worth metallic nanomaterial due to their biocompatibility, low cytotoxicity compared to other nanomaterials, higher and ease of detection along with the capability of functionalization. It has been reported to damage cell membrane by changing membrane potential which leads to ATP loss and oxidative stress which further causes ROS generation resulting in microbial death (Abdel-Raouf et al. 2017). It is also used as a carrier in drug delivery by the ease of

functionalization with thiol groups, low cytotoxicity and surface Plasmon resonance properties. Thus, biocompatibility, conjugation with functional groups, high absorption and optical properties help in targeted drug delivery and therapeutics (Chen et al. 2008). The size of Au nanoparticles is less than 2 mm; therefore, several studies speculate on the antimicrobial activity of Au nanoparticles. Au nanoparticlesuse as anticancer or antibacterial agents is due to irradiation with laser energy with the help of electrons which generate heat by excitation and oscillation (Riley and Day 2017).

2.1.5 Copper (Cu) Nanoparticles

Copper (Cu) nanoparticlesare amongst the best antimicrobial agents due to their chemical stability and resistance to heat. Cu nanoparticles are evaluated for the antibacterial and antifungal activities on various microorganisms which include *P. aeruginosa, S. aureus, Salmonella choleraesuis, C. albicans* and *B. subtilis* (Dizaj et al., 2014). Whereas, due to the rapid rate of oxidation Cu nanoparticles are not widely used. Therefore, Copper nanoparticles can be synthesised as copper oxides nanoparticles and copper nanoparticles loaded thin film which interacts with carboxyl and amine groups of the membrane of the microbial cell along with induces ROS with inhibits replication of DNA and protein synthesis (Blecher et al. 2011). Copper oxide (CuO) is a more cost efficient antimicrobial when compared with Ag and Au. It is more stable, both physically and chemically in relation to the others. It also possesses properties for easy miscible with the polymers (Huh and Kwon 2011).

2.1.6 Aluminium Oxide Nanoparticles (Al_2O_3)

The antimicrobial effect due to $Al_2O_3$is limited to mild inhibitory effect, it is also at high concentration, by disrupting cell wall. These nanoparticles are supposed to cause resistance in microbes (Qiu et al. 2012). In *E. coli*, Al_2O_3 nanoparticles travel through the cytoplasm and result in toxic effect (Hajipour et al. 2012). Their higher concentrations damages the cell wall but studies report that it only causes a low level of growth inhibition (Huh and Kwon 2011). Al_2O_3 nanoparticles increase the risk of horizontal gene transfer by 200-folds through conjugation especially in *E. coli* and *Salmonella* (Qiu et al. 2012). It damages the microbes through oxidative stress and promotes the expression of genes involved in conjugation along with suppression of genes that inhibit conjugation (Huh and Kwon 2011; Qiu et al. 2012).

2.1.7 Magnesium (Mg) Nanoparticles

Magnesium halogen conjugates and magnesium oxide (MgO) nanoparticles are the two types of magnesium-based nanoparticles used as the antimicrobial therapeutics. Magnesium halogen-containing nanoparticles act by inhibiting microbial enzymes while MgO containing nanoparticles work by ROS production leading to lipid peroxidation of the microbial cell membrane which leads to an outflow of cytoplasmic

contents. For example, MgF_2nanoparticles work by lipid peroxidation of the microbial cell membrane leading to efflux of cytoplasmic contents along with a drop in cytoplasmic pH which thereby increases the membrane potential. MgF_2 has been successfully studied against *E. coli* and *S. aureus* for growth inhibition and prevent biofilm formation (Blecher et al. 2011).

2.1.8 Bismuth Nanoparticles (Bi)

Bi nanoparticles are effective against multi-drug resistant microbes when combined with X-rays thereby limiting the toxic effect on the host cells (Luo et al. 2013).When combined with X-rays Bi nanoparticles emits free radicals and electrons, these damages the bacterial DNA. These are effective against *P. aeruginosa* (Luo et al., 2013).

2.1.9 Calcium Nanoparticles (Ca)

CaO nanoparticles have strong antimicrobial activity, due to free and active oxygen species. According to the study by Jeong et al., antimicrobial CaO can be generated by heating $CaCO_3$ (Jeong et al. 2007). The mechanism of action of CaO is similar to MgO by acting on the cell wall. Due to increased oxidative stress and the generation of superoxide anions, the antimicrobial effect occurs. The other reason for antimicrobial activity is due to an increase in pH (Dizaj et al. 2014).

2.1.10 Silicon (Si) Nanoparticles

Antimicrobial action of SiO_2 nanoparticles would turn out to be more noteworthy due to more surface area. Si nanoparticles conjugated with the other biocidal metals, for example, Ag has been widely examined, Egger et al. announced the creation and examination of antimicrobial action of novel Ag–Si nanocomposite (Egger et al. 2009).The results suggest that Ag/SiO2 nanocomposites showed enhanced antimicrobial properties against *E. coli, S. aureus*, and *C. albicans.* The applications of nanocomposites are endless as it can be mixed and prepared with antimicrobial activity.

2.2 Non-metallic Nanomaterial

2.2.1 Hydrogel-Based Nanomaterial

These nitric oxide-releasing nanomaterials have antimicrobial potential against the broad spectrum of multi-drug resistant microbes. They are effective against multi-drug resistant *S.aureus* (MRSA), *A. baumannii* (Friedman et al., 2008). They

increase the synthesis of interferon-ɣ, which inhibits angiogenesis in reducing the spread of microbes (Han et al. 2009). Later on, a study by Friedman et al., reports that when nitric oxide-releasing hydrogel when reacts with glutathione (GSH) produced S-nitrosoglutathione significantly decreases the microbial growth of MRSA, *E. coli*, *P. aeruginosa*, and *K. pneumonia* in comparison to independent inhibition by hydrogel or GSH (Friedman et al. 2011).

2.2.2 Chitosan-Based Nanomaterial

Chitosan is deacetylated monomeric units of chitin in a random manner derived from a polymeric chain of N- acetyl glucosamine and glucosamine (Huh and Kwon 2011). From the deacetylated units every C2 amino group of chitosan has pKa of 6.5 leading to protonation and pH lower than 6.5 which is associated with antimicrobial and anti-inflammatory properties of Chitosan (Friedman et al. 2013). The positive charge of Chitosan provides affinity towards negatively charged cell wall and cell membrane of microbes. This increases the influx in cell envelope causing osmotic damage, efflux of cytoplasmic contents (Friedman et al. 2013). It is unlikely to develop resistance against chitosan-based nanomaterial as the cell envelope of microbes is highly conserved to evolutionary changes so, it does not change with a single gene mutation. It also acts by inhibiting the mRNA during transcription, preventing growth and metabolic activities of the microbes especially in bacteria and fungus (Friedman et al. 2013). It reduces the activity of metalloproteins as chitosan chelates metals. By inhibiting secretion of inflammatory cytokines, it employees fibroblast cells and deposits collagen III, thereby promoting faster wound healing and prevents infection of wounds. Chitosan nanomaterial is effective against *S. aureus* in comparison to E. coli. It has been reported to have stronger activity against fungi and viruses compared to bacteria (Blecher et al. 2011). Nano-chitosan with low molecular weight has greater efficiency against gram-positive bacteria than gram-negative bacteria. Although, chitosan would be more effective against Gram-negative bacteria because of the presence of more negative charged cell envelope. Positively charged amino groups of chitosan have the ability to replace Ca2+ and Mg2+ ions involved in destabilizing the lipopolysaccharide of gram-negative bacteria which increases the permeability of the membrane (Friedman et al. 2013). Chitosannanoparticles are biodegradable antimicrobial nanoparticles which can be employed as an agent to combat antimicrobial resistance. The biodegradable nanoparticles are more advantageous as antimicrobial metal and metal oxide nanoparticle could not be used due to increased accumulation and toxicity.

2.2.3 Graphene, Carbon Nanotubes and Fullerenes

Graphene nanomaterial includes oxides, reduced oxides and nano-composites which are based on antimicrobial activity due to their surface properties, sheet effect leading to cell dysfunction and oxidative stress in the cell (Ocsoy et al. 2017). The

layer-by-layer assembly of graphene oxide nanosheets attributes to: optical, dielectric and antibacterial aspects (Baranwal et al. 2018). The property to prevent microbial contamination, graphene-based nanomaterial can be employed in food packaging. Single-walled carbon nanotubes (SWCNTs) have been found efficient against both gram-negative and gram-positive bacteria as they are toxic to microbes which further disrupts membrane integrity along with induces oxidative stress (Dizaj et al. 2014). Therefore, carbon nanotubes (CNTs) have been used in filters to prevent bio-fouling and biofilm formation (Lee et al. 2010). The microbicidal property of fullerenes (C60) and its derivatives like fullerol has not yet been exploited much but is attributed to ROS generation and highly reactive singlet oxygen species formation respectively (Lyon et al. 2006).

2.2.4 Organic Nanomaterial

In the last few decades, a group of nanomaterial has attracted considerable interest including dendrimeric peptides, liposomes, polymer-based nanomaterial etc. A dendrimeric peptide containing multiple R (Arg) W (Trp) dipeptides synthesised against gram-negative and gram-positive bacteria which act via membranolytic method (Liu et al. 2007). G3KL, a novel antimicrobial dendrimeric peptide containing alternating branches of natural leucine and lysine amino acids effective against A. baumannii and P. aeruginosa as compared to standard antibiotics (Pires et al. 2015). A tetra-branched SB105 potentially inhibited replication of human cytomegalovirus (HCMV) strains in primary fibroblast and endothelial cells. Dendrimer SB105 prevents virions attachment to heparansulphate over the cell membrane (Luganini et al. 2010). The microbicidal properties of dendrimeric peptides are due to high surface area ratio, in vivo activity, affinity to carry both polar and non-polar drug molecules (Cheng et al. 2016).

Liposomes have been used since long as cargos of the drug due to their ability to mimic microbial cell membrane, which allows them to fuse with the infectious microbes. Thereby, allows unhindered delivery of the drug in the cell which causes oxidative stress and imbalanced ionic levels leading to cell death (Pushparaj Selvadoss et al. 2018). Similarly, polymer nanomaterial due to a stable structure, zeta potential, affinity to cargo drugs allows delivery of antimicrobial agents.

2.2.5 Polymer Nanomaterial

By imitating the general compound structure of antimicrobial peptides, polymers could be synthesised with antimicrobial characteristics by fusing cationic and hydrophobic moieties into the polymer chains. Interaction with the bacterial cell walls which possess negative chargetooccur due to the general cationic charge present on the polymer, while the hydrophobic partners enable the penetration inside the microbial membrane (Lam et al. 2017). The polymeric nanoparticles can be of various types on the basis of its architecture, such as self-assembly polymer

nanoparticles and star nanoparticles. The type of antimicrobial activity is contributed by the type of polymeric nanomaterial and its specific characteristics. Polymer nanoparticlesare also useful for antimicrobial drug delivery due to its stable structure which enables the synthesis of nanoparticles with nano-size distribution, particle properties which can be specified by the selection of surfactant, organic solvent and the length of the polymer and presence of functional group on the polymer nanoparticles which can be chemically modified (Lakshminarayanan et al. 2018).

3 Application of Nanomaterial as Antimicrobial Agent

Nanoparticle obtained from either physical, chemical, or biological method as mentioned in (Table 2) consist of various applications. Nanoparticle possesses various application as antimicrobials such as water disinfectant, therapeutic, food packaging preserver, drug delivery agent, nano-fertilizer and nano-pesticides, antibacterial paper, antibacterial textile, biofortification and biodegradable nanoparticle for environment protection. For e.g., nanotechnology has provided alternative way for water disinfection. Nanomaterial result as an effective antimicrobial due to the high surface-to-volume ratio, crystallographic structure, and adaptability to various substrates. Several metal and metal oxide nanoparticles have been applied to the use of water disinfection. Silver nanoparticle (AgNP) are the most utilised nanoparticle for water disinfection (Liu et al. 2012). Another antimicrobial used as water

Table 2 Advantages and disadvantages of nanoparticle synthesis method

Method	Advantages	Disadvantages
Physical method	The solute system is not present	Not environment friendly
	Desirable size and shape of the nanoparticle can be obtained	Huge infrastructure required
	Interaction domains can be modified	More time consuming
	Utilize bulky nanoparticle	
Chemical method	Can be combined with the physical method	Hazardous chemicals involved
	Solution can be aqueous and non-aqueous	Accumulation of nanoparticle can occur
		Sometimes particle may not stabilize
		Not environment friendly
Biological method	Environment friendly	To be monitored
	Size and shape of the nanoparticle can be monitored	Media constituents
	No chemicals required	Environmental conditions,
	Cost-effective	Genetic makeup,
	Renewable synthesis	Cell growth conditions,
	Large scale synthesis	Enzyme activity

disinfectant is TiO_2 by causing ROS burden on microbial cells. Advantage of using TiO_2 for water disinfection include stability of TiO_2 in water and ingestion has low toxicity to human health (Liu et al. 2012).

4 Toxicity of Nanomaterial

Nanotechnology has increased critical advancement over the previous decades, which steer the revolution in the sphere of information, industry, medicine, aerospace aviation and food security. Nanotechnology has become a new research hot spot in the world. However, we cannot only focus to its benefits to the society and economy because its increased use has been creating potent environmental and health effects due to the toxicity of the nanoparticles. At high doses, anything to everything can be toxic but it is relevant to understand the ideal concentration of nanomaterial to be used. The toxicity of nanomaterials is determined by the base material, size, shape and coatings.

For toxicity studies, several research groups use distinct cell lines, culture environment and incubation periods. It is difficult to determine physiologically relevant cytotoxicity due to difference in toxicity parameters during the study by different groups. To understand the toxic effect several biological models includes cell lines, aquatic embryonic zebrafish (*Danio rerio*), and whole-animal tests such as rodents (mice/rat) (Girardi et al. 2017; Griffitt et al. 2007).

5 Metal Nanomaterial

Metallic nanoparticles are most extensively used engineered nanomaterials; however, there is limited understanding in context with environmental fate and effects. Comparatively bulk gold is safe, due to its remarkable characteristics; different researchers have evaluated cellular uptake and toxicity of gold nanoparticles. In the study by Goodman et al. reported non- cytotoxic effect of gold nanoparticles with immune system cells and reduction in harmful ROS in the cells. Their study in three different types of cells suggested the toxicity of 2 nm gold nanoparticles functionalized with both cationic and anionic surface groups which proved that cationic functionalization is less toxic than anionic particles, which might be attributed to the electrostatic interaction between the cationic group of nanomaterial and the negatively charged cell membrane (Goodman et al. 2004). Nanomaterial may show less or no cytotoxicity but may cause serious cellular damage.

Cytotoxicity is related to cell type; 33 nm citrate-capped gold nanospheres were non-cytotoxic in baby hamster kidney and human hepatocellular liver carcinoma cells, but cytotoxic to a human carcinoma lung cell line as reported by Patra et al. (2007).

Prolonged exposure to silver results in argyria marked by a blue-gray discoloration of the skin and other organs. Low-level exposure can lead silver deposition on

skin and other parts of the body. Elevated levels of silver in air can cause breathing problems, lung and throat irritation, and stomach pain, mild allergic reactions over skin including rashes, swelling, and inflammation (Drake and Hazelwood 2005).

Griffitt et al. reported toxicity of metallic nanomaterial in aquatic organisms (zebrafish, daphnids and an algal species) Different organisms manifested with silver, copper, aluminium, nickel, and cobalt as both nanoparticles and soluble salts as well as to titanium dioxide nanoparticles resulted in nanosilver and nano-copper toxicity with 48-h lethal concentrations as low as 40 and 60 μg/L, respectively, in *Daphnia pulex* adults, whereas titanium dioxide was non-toxic (Griffith and Swartz 2006).

5.1 Metal Oxide Nanomaterial

These nanomaterial are vitally utilized as added substances in pharmaceuticals, beauty care products and colouring agents. TiO_2/ZnO based nanomaterial have water and strain resistant properties, so are used in sunscreens and stringy creams. A few studies have analyzed the detrimental effects of metal oxide nanomaterial.

A study by Grassian et al. reported 2–5 nm TiO_2 nanomaterial inhalation exposure and their aggregation for the formation of aerosols in the exposure chamber (Grassian et al. 2007). A significant inflammatory response was observed in mice, 3 weeks post subacute exposure to the aggregates (Fabian et al. 2008).

Much has not been reported regarding impact of nanomaterial on higher plants.

Nano-TiO_2 remarkably enhances photosynthesis and spinach development by boosting nitrogen fixation. Suspension of nano-alumina had no impact on California red kidney bean and ryegrass development (Wang et al. 2011). However, it prevents rooting in corn, cucumber, soybean, cabbage, and carrot. High concentration of nano-ferrophase obstructed popcorn development. Lin et al. analyzed nano-ZnO cell internalization and upward translocation in Loliumperenne (ryegrass) (Lin and Xing 2008). Scanning electron microscopy and transmission electron microscopy were used to demonstrate internalization of ZnO nanoparticles, ryegrass biomass loss, root tips shrinking and root epidermal and cortical cells vacuolation. During translocation of Zn from root to shoot does not attribute to risk in use of nano-ZnO (Lin and Xing 2008).

Franklin et al. stated relative toxicity of nano-ZnO, bulk ZnO, and $ZnCl_2$ in freshwater microalgae i.e. *Pseudokirchneriella subcapitata* (Franklin et al., 2007). This revealed the toxicity in 72 h with IC_{50} near 60 μg Zn/L (Franklin et al. 2007).

Karlsson et al. focused metal oxide nanoparticles (CuO, TiO_2, ZnO, $CuZnFe_2O_4$, Fe_3O_4, Fe_2O_3) and differentiated with carbon nanoparticles and multi-walled carbon nanotubes (MWCNT). This concluded that a various nanoparticles have different toxicities (Karlsson et al. 2008). CuO nanoparticles are prone to cytotoxicity and DNA damage (Chang et al. 2012). ZnO indicate effects viability of cells and caused DNA damage (Chang et al. 2012), while the TiO_2 particles (a blend of rutile and anatase) cause DNA damage (Zhu et al. 2010). In metal oxide nanomaterial (Fe_3O_4,

Fe_2O_3), no or low toxicity has been observed, however, $CuZnFe_2O_4$ particles leads to DNA injuries (Karlsson et al. 2008). Also, carbon nanotubes present cytotoxicity and cause DNA mutations. Xia et al. stated ROS and cytotoxicity of TiO_2, ZnO, and CeO_2, in RAW 264.7 and BEAS-2B cell lines which concluded that ZnO instigates lethality in both, leading to ROS, oxidant damage and cell death (Xia et al. 2006). Conversely, cellular uptake of nano-CeO_2 in low concentrations is genotoxic and produces ROS and oxidative stress (Zeyons et al. 2009).

5.2 Carbon Nanomaterial

Siliva et al. proved that ultrafine carbon particles effectively penetrate lungs compared to larger particles and have the ability to cross the blood-brain barrier leading to central nervous system (CNS) toxicity. This also proved that inhalation of CNTs can result in CNS toxicity rather releasing clotting agents from the lungs (Silva et al. 2011). Asbestoes fibre inhalation induces asbestosis, lung cancer, and malignant mesothelioma of pleura. Thus, asbestos is highly lethal than CNT due to their structural resemblances (Magrez et al. 2006).

Zhu et al. studied multi-walled carbon nanotubes (MWCNTs) in mouse embryonic stem (ES) cells for DNA damage. It was found that MWNTs accumulates and induces apoptosis by activating the tumor suppressor protein p53 in 2 h exposure. It also induces oxidative stress They also report elevated expression base excision repair protein 8-oxoguanine-DNA glycosylase 1 (OGG1), double-strand break repair protein Rad 51, phosphorylation of H2AX histone at serine 139, and SUMO modification of XRCC4 after treating with MWCNTs (Zhu et al. 2007).

5.3 Quantum Dots

Quantum Dots (QDs) are characterized by unique optical and electrical properties which furnish QDs as optimal fluorophores for biomedical imaging/diagnosis, e.g. fluorescent QDs conjugated with bioactive of DNA, protein and cell membrane receptors moieties to target specific process. Different QD have specific physicochemical properties, which determines potential toxicity.

Zhang et al. reported the impact of QDs via skin penetration. Their study accounted carboxylic acid coated QD655 and QD565 diffused in uppermost stratum corneum layer of skin, with constant flow of 8 and 24 h, proves to be cytotoxic (Zhang et al 2008).

Shiohara et al. also reported QD-induced cytotoxicity. 11-mercaptoundecanoic acid (MUA)-coated CdSe/ZnS QDs were cytotoxic to HeLa cell lines and primary human hepatocytes at 100 μg/mL (MTT assay) concentration. Using primary hepatocytes as a liver model, Deufus et al. found that CdSe-core QDs induced acute toxicity.

This study also proved that QDs cytotoxicity varies due to synthesis parameters, ultraviolet light exposure and surface coating. This suggests that cytotoxicity related to release of free Cd^{2+} ions because of CdSe lattice deterioration (Shiohara et al. 2004).

6 Summary, Outlook and Future Needs

In summary, we have discussed the types, behaviour, applications and toxicity of several nanomaterials in use. The toxic effect of nanomaterials has been studied but much is not known yet. Also, there is lack of knowledge, how nanomaterials interact with the environmental system. More research is required evaluate their stability in different test systems identify prospects for human use. Studies relating toxicity on diverse cell lines with varying incubation times are being reported, but divergent nanoparticle concentrations, cell lines as well as culture conditions results in poor lack knowledge of their mechanism, relevance of toxicity. Nevertheless, as per the above discussion, numerous research challenges within this field remain answered. Once the biomedical society acknowledges nanomaterials as tool for biomedical imaging, for future, only then their interaction with cells and organs will be understood.

Analytical methods can be employed for better understanding, the formation and activity mechanism of nanomaterials. Along with, the importance of nanomaterial purity is detected by analytical methods to identify impurities, appreciating the use of greener approaches. Indeed, they are too small to be detected by optical microscopes. The challenge is to reach global agreement on a battery of in vitro screening tests for human and environmental toxicity.

To control size and shape of the nanomaterials, surfactants used are toxic. Therefore, one of the aim is to identify alternatives to the use of surfactants or other substances for nanomaterial stability and shape during synthesis. New biomimetic approaches are pivotal to control shape are essential, which are promising biological derivatives for nanoparticle production. Intense work is required for the development of these methods. Green nanoscience guides design, production, and application of greener nanomaterials with broad spectrum compositions, sizes, shapes, and functionality. This will provide research opportunities and challenges for this community in the foreseeable future.

Imparting research on nanotechnology risks and advantages outside mainstream researchers is challenging, however, is fundamental for exchanges in light of sound science. This implies creating correspondence exercises that empower specialized data to be condensed, scrutinized and at last integrated for different invested individuals, including chiefs and customers. At last, a worldwide comprehension of nanotechnology-particular danger is fundamental assuming extensive and little businesses work on a level playing field, and creating economies are not to be denied basic data on planning safe nanotechnologies. If universally research community can take benefit of these circumstances then we can surely look towards the advent of safe nanotechnologies.

References

Abdel-Raouf, N., Al-Enazi, N. M., & Ibraheem, I. B. (2017). Green biosynthesis of gold nanoparticles using Galaxaura elongata and characterization of their antibacterial activity. *Arabian Journal of Chemistry, 10*, S3029–S3039.

Akhtar, M. J., Ahamed, M., Kumar, S., Khan, M. M., Ahmad, J., & Alrokayan, S. A. (2012). Zinc oxide nanoparticles selectively induce apoptosis in human cancer cells through reactive oxygen species. *International Journal of Nanomedicine, 7*, 845.

Allahverdiyev, A. M., Abamor, E. S., Bagirova, M., & Rafailovich, M. (2011). Antimicrobial effects of TiO2 and Ag2O nanoparticles against drug-resistant bacteria and leishmania parasites. *Future Microbiology, 6*(8), 933–940.

Andreini, C., Bertini, I., Cavallaro, G., Holliday, G. L., & Thornton, J. M. (2008). Metal ions in biological catalysis: From enzyme databases to general principles. *Journal of Biological Inorganic Chemistry, 13*(8), 1205–1218.

Armentano, I., Arciola, C. R., Fortunati, E., Ferrari, D., Mattioli, S., Amoroso, C. F., … Visai, L. (2014). The interaction of bacteria with engineered nanostructured polymeric materials: A review. *The Scientific World Journal, 2014*.

Ansari, H., Shabanian, M., & Khonakdar, H. A. (2017). Using a β-Cyclodextrin-functional Fe3O4 as a Reinforcement of PLA: Synthesis, Thermal, and Combustion Properties. *Polymer-Plastics Technology and Engineering, 56*(12), 1366–1373.

Avalos, A., Haza, A. I., Mateo, D., & Morales, P. (2016). Interactions of manufactured silver nanoparticles of different sizes with normal human dermal fibroblasts. *International Wound Journal, 13*(1), 101–109.

Bahri-Laleh, N., Correa, A., Mehdipour-Ataei, S., Arabi, H., Haghighi, M. N., Zohuri, G., … Cavallo, L. (2011). Moving up and down the titanium oxidation state in Ziegler– Natta catalysis. *Macromolecules, 44*(4), 778–783.

Baranwal, A., Srivastava, A., Kumar, P., Bajpai, V. K., Maurya, P. K., & Chandra, P. (2018). Prospects of nanostructure materials and their composites as antimicrobial agents. *Frontiers in Microbiology, 9*, 422.

Blecher, K., Nasir, A., & Friedman, A. (2011). The growing role of nanotechnology in combating infectious disease. *Virulence, 2*(5), 395–401.

Chang, Y.-N., Zhang, M., Xia, L., Zhang, J., & Xing, G. (2012). The toxic effects and mechanisms of CuO and ZnO nanoparticles. *Materials, 5*(12), 2850–2871.

Chen, P. C., Mwakwari, S. C., & Oyelere, A. K. (2008). Gold nanoparticles: From nanomedicine to nanosensing. *Nanotechnology, Science and Applications, 1*, 45.

Cheng, G., Dai, M., Ahmed, S., Hao, H., Wang, X., & Yuan, Z. (2016). Antimicrobial drugs in fighting against antimicrobial resistance. *Frontiers in Microbiology, 7*, 470.

Chupani, L., Zusková, E., Niksirat, H., Panáček, A., Lünsmann, V., Haange, S.-B., … Jehmlich, N. (2017). Effects of chronic dietary exposure of zinc oxide nanoparticles on the serum protein profile of juvenile common carp (*Cyprinus carpio* L.). *Science of the Total Environment, 579*, 1504–1511.

Chwalibog, A., Sawosz, E., Hotowy, A., Szeliga, J., Mitura, S., Mitura, K., … Sokolowska, A. (2010). Visualization of interaction between inorganic nanoparticles and bacteria or fungi. *International Journal of Nanomedicine, 5*, 1085.

Dizaj, S. M., Lotfipour, F., Barzegar-Jalali, M., Zarrintan, M. H., & Adibkia, K. (2014). Antimicrobial activity of the metals and metal oxide nanoparticles. *Materials Science and Engineering: C, 44*, 278–284.

Drake, P. L., & Hazelwood, K. J. (2005). Exposure-related health effects of silver and silver compounds: A review. *The Annals of Occupational Hygiene, 49*(7), 575–585.

Egger, S., Lehmann, R. P., Height, M. J., Loessner, M. J., & Schuppler, M. (2009). Antimicrobial properties of a novel silver-silica nanocomposite material. *Applied and Environmental Microbiology, 75*(9), 2973–2976.

Espitia, P. J. P., Soares, N. D. F. F., Teófilo, R. F., dos Reis Coimbra, J. S., Vitor, D. M., Batista, R. A., … Medeiros, E. A. A. (2013). Physical–mechanical and antimicrobial properties of nanocomposite films with pediocin and ZnO nanoparticles. *Carbohydrate Polymers, 94*(1), 199–208.

Fabian, E., Landsiedel, R., Ma-Hock, L., Wiench, K., Wohlleben, W., & Van Ravenzwaay, B. (2008). Tissue distribution and toxicity of intravenously administered titanium dioxide nanoparticles in rats. *Archives of Toxicology, 82*(3), 151–157.

Fernando, S., Gunasekara, T., & Holton, J. (2018). Antimicrobial nanoparticles: Applications and mechanisms of action. *Sri Lankan Journal of Infectious Diseases, 8*(1), 2–11.

Franklin, N. M., Rogers, N. J., Apte, S. C., Batley, G. E., Gadd, G. E., & Casey, P. S. (2007). Comparative toxicity of nanoparticulate ZnO, bulk ZnO, and ZnCl2 to a freshwater microalga (Pseudokirchneriella subcapitata): The importance of particle solubility. *Environmental Science & Technology, 41*(24), 8484–8490.

Friedman, A. J., Han, G., Navati, M. S., Chacko, M., Gunther, L., Alfieri, A., & Friedman, J. M. (2008). Sustained release nitric oxide releasing nanoparticles: Characterization of a novel delivery platform based on nitrite containing hydrogel/glass composites. *Nitric Oxide, 19*(1), 12–20.

Friedman, A. J., Blecher, K., Schairer, D., Tuckman-Vernon, C., Nacharaju, P., Sanchez, D., … Nosanchuk, J. D. (2011). Improved antimicrobial efficacy with nitric oxide releasing nanoparticle generated S-nitrosoglutathione. *Nitric Oxide, 25*(4), 381–386.

Friedman, A. J., Phan, J., Schairer, D. O., Champer, J., Qin, M., Pirouz, A., … Modlin, R. L. (2013). Antimicrobial and anti-inflammatory activity of chitosan–alginate nanoparticles: A targeted therapy for cutaneous pathogens. *Journal of Investigative Dermatology, 133*(5), 1231–1239.

Girardi, F. A., Bruch, G. E., Peixoto, C. S., Dal Bosco, L., Sahoo, S. K., Gonçalves, C. O., … Barros, D. M. (2017). Toxicity of single-wall carbon nanotubes functionalized with polyethylene glycol in zebrafish (*Danio rerio*) embryos. *Journal of Applied Toxicology, 37*(2), 214–221.

Goodman, C. M., McCusker, C. D., Yilmaz, T., & Rotello, V. M. (2004). Toxicity of gold nanoparticles functionalized with cationic and anionic side chains. *Bioconjugate Chemistry, 15*(4), 897–900.

Grassian, V. H., O'Shaughnessy, P. T., Adamcakova-Dodd, A., Pettibone, J. M., & Thorne, P. S. (2007). Inhalation exposure study of titanium dioxide nanoparticles with a primary particle size of 2 to 5 nm. *Environmental Health Perspectives, 115*(3), 397.

Griffith, L. G., & Swartz, M. A. (2006). Capturing complex 3D tissue physiology in vitro. *Nature Reviews Molecular Cell Biology, 7*(3), 211.

Griffitt, R. J., Weil, R., Hyndman, K. A., Denslow, N. D., Powers, K., Taylor, D., & Barber, D. S. (2007). Exposure to copper nanoparticles causes gill injury and acute lethality in zebrafish (*Danio rerio*). *Environmental Science & Technology, 41*(23), 8178–8186.

Gunalan, S., Sivaraj, R., & Rajendran, V. (2012). Green synthesized ZnO nanoparticles against bacterial and fungal pathogens. *Progress in Natural Science: Materials International, 22*(6), 693–700.

Hajipour, M. J., Fromm, K. M., Ashkarran, A. A., de Aberasturi, D. J., de Larramendi, I. R., Rojo, T., … Mahmoudi, M. (2012). Antibacterial properties of nanoparticles. *Trends in Biotechnology, 30*(10), 499–511.

Han, G., Martinez, L. R., Mihu, M. R., Friedman, A. J., Friedman, J. M., & Nosanchuk, J. D. (2009). Nitric oxide releasing nanoparticles are therapeutic for *Staphylococcus aureus* abscesses in a murine model of infection. *PLoS One, 4*(11), e7804.

Hsueh, P.-R. (2010). New Delhi metallo-β-lactamase-1 (NDM-1): An emerging threat among Enterobacteriaceae. *Journal of the Formosan Medical Association, 109*(10), 685–687.

Huang, L., Dai, T., Xuan, Y., Tegos, G. P., & Hamblin, M. R. (2011). Synergistic combination of chitosan acetate with nanoparticle silver as a topical antimicrobial: Efficacy against bacterial burn infections. *Antimicrobial Agents and Chemotherapy, 55*(7), 3432–3438.

Huh, A. J., & Kwon, Y. J. (2011). "Nanoantibiotics": A new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. *Journal of Controlled Release, 156*(2), 128–145.

Jadhav, S., Gaikwad, S., Nimse, M., & Rajbhoj, A. (2011). Copper oxide nanoparticles: synthesis, characterization and their antibacterial activity. *Journal of Cluster Science, 22*(2), 121–129.

Jeong, M. S., Park, J. S., Song, S. H., & Jang, S. B. (2007). Characterization of antibacterial nanoparticles from the scallop, Ptinopecten yessoensis. *Bioscience, Biotechnology, and Biochemistry, 71*(9), 2242–2247.

Jiang, W., Mashayekhi, H., & Xing, B. (2009). Bacterial toxicity comparison between nano-and micro-scaled oxide particles. *Environmental pollution, 157*(5), 1619–1625.

Karlsson, H. L., Cronholm, P., Gustafsson, J., & Moller, L. (2008). Copper oxide nanoparticles are highly toxic: A comparison between metal oxide nanoparticles and carbon nanotubes. *Chemical Research in Toxicology, 21*(9), 1726–1732.

Kumar, B. N. P., Mahaboobi, S., & Satyam, S. (2017). Chitosan in Medicine–A Mini Review. *J Mol Pharm Org Process Res, 5*(134), 2.

Lakshminarayanan, R., Ye, E., Young, D. J., Li, Z., Loh, X. J. (2018). Recent advances in the development of antimicrobial nanoparticles for combating resistant pathogens. *Advanced Healthcare Materials,* 1701400.

Lam, S. J., Wong, E. H., Boyer, C., & Qiao, G. G. (2017). Antimicrobial polymeric nanoparticles. *Progress in Polymer Science, 63*, 561–570.

Lara, H. H., Ayala-Núñez, N. V., Turrent, L. D. C. I., & Padilla, C. R. (2010). Bactericidal effect of silver nanoparticles against multidrug-resistant bacteria. *World Journal of Microbiology and Biotechnology, 26*(4), 615–621.

Lee, J., Mahendra, S., & Alvarez, P. J. (2010). Nanomaterials in the construction industry: A review of their applications and environmental health and safety considerations. *ACS Nano, 4*(7), 3580–3590.

Lin, D., & Xing, B. (2008). Root uptake and phytotoxicity of ZnO nanoparticles. *Environmental Science & Technology, 42*(15), 5580–5585.

Liu, Z., Young, A. W., Hu, P., Rice, A. J., Zhou, C., Zhang, Y., & Kallenbach, N. R. (2007). Tuning the membrane selectivity of antimicrobial peptides by using multivalent design. *ChemBioChem, 8*(17), 2063–2065.

Liu, Y., He, L., Mustapha, A., Li, H., Hu, Z. Q., & Lin, M. (2009). Antibacterial activities of zinc oxide nanoparticles against Escherichia coli O157: H7. *Journal of applied microbiology, 107*(4), 1193–1201.

Liu, C., Xie, X., & Cui, Y. (2012). Antimicrobial nanomaterials for water disinfection. In *Nano-antimicrobials* (pp. 465–494). Heidelberg: Springer.

Luganini, A., Giuliani, A., Pirri, G., Pizzuto, L., Landolfo, S., & Gribaudo, G. (2010). Peptide-derivatized dendrimers inhibit human cytomegalovirus infection by blocking virus binding to cell surface heparan sulfate. *Antiviral Research, 85*(3), 532–540.

Luo, Y., Hossain, M., Wang, C., Qiao, Y., An, J., Ma, L., & Su, M. (2013). Targeted nanoparticles for enhanced X-ray radiation killing of multidrug-resistant bacteria. *Nanoscale, 5*(2), 687–694.

Lyon, D. Y., Adams, L. K., Falkner, J. C., & Alvarez, P. J. (2006). Antibacterial activity of fullerene water suspensions: Effects of preparation method and particle size. *Environmental Science & Technology, 40*(14), 4360–4366.

Magrez, A., Kasas, S., Salicio, V., Pasquier, N., Seo, J. W., Celio, M., … Forró, L. (2006). Cellular toxicity of carbon-based nanomaterials. *Nano Letters, 6*(6), 1121–1125.

Ocsoy, I., Temiz, M., Celik, C., Altinsoy, B., Yilmaz, V., & Duman, F. (2017). A green approach for formation of silver nanoparticles on magnetic graphene oxide and highly effective antimicrobial activity and reusability. *Journal of Molecular Liquids, 227*, 147–152.

Organization, W. H. (2016). *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach*. Geneva: World Health Organization.

Organization, W. H. (2018). High levels of antibiotic resistance found worldwide, new data shows. *Saudi Medical Journal, 39*(4), 430–431.

Patra, H. K., Banerjee, S., Chaudhuri, U., Lahiri, P., & Dasgupta, A. K. (2007). Cell selective response to gold nanoparticles. *Nanomedicine: Nanotechnology, Biology and Medicine, 3*(2), 111–119.

Pires, J., Siriwardena, T. N., Stach, M., Tinguely, R., Kasraian, S., Luzzaro, F., … Endimiani, A. (2015). In vitro activity of the novel antimicrobial peptide dendrimer G3KL against multidrug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa. *Antimicrobial Agents and Chemotherapy, 59*(12), 7915–7918.

Pushparaj Selvadoss, P., Nellore, J., Balaraman Ravindrran, M., Sekar, U., & Tippabathani, J. (2018). Enhancement of antimicrobial activity by liposomal oleic acid-loaded antibiotics for the treatment of multidrug-resistant Pseudomonas aeruginosa. *Artificial Cells, Nanomedicine, and Biotechnology, 46*(2), 268–273.

Qi, L., Xu, Z., Jiang, X., Hu, C., & Zou, X. (2004). Preparation and antibacterial activity of chitosan nanoparticles. *Carbohydrate research, 339*(16), 2693–2700.

Qiu, Z., Yu, Y., Chen, Z., Jin, M., Yang, D., Zhao, Z., … Qian, D. (2012). Nanoalumina promotes the horizontal transfer of multiresistance genes mediated by plasmids across genera. *Proceedings of the National Academy of Sciences, 109*(13), 4944–4949.

Riley, R. S., & Day, E. S. (2017). Gold nanoparticle-mediated photothermal therapy: Applications and opportunities for multimodal cancer treatment. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 9*(4), e1449.

Schwartz, B., Bell, D. M., & Hughes, J. M. (1997). Preventing the emergence of antimicrobial resistance: A call for action by clinicians, public health officials, and patients. *JAMA, 278*(11), 944–945.

Scorciapino, M. A., Serra, I., Manzo, G., & Rinaldi, A. C. (2017). Antimicrobial dendrimeric peptides: structure, activity and new therapeutic applications. *International journal of molecular sciences, 18*(3), 542.

Shiohara, A., Hoshino, A., Hanaki, K., Suzuki, K., & Yamamoto, K. (2004). On the cytotoxicity caused by quantum dots. *Microbiology and Immunology, 48*, 669–675.

Silva, L. F., Oliveira, M. L., Neace, E. R., O'Keefe, J. M., Henke, K. R., & Hower, J. C. (2011). Nanominerals and ultrafine particles in sublimates from the Ruth Mullins coal fire, Perry County, Eastern Kentucky, USA. *International Journal of Coal Geology, 85*(2), 237–245.

Simon-Deckers, A., Loo, S., Mayne-L'hermite, M., Herlin-Boime, N., Menguy, N., Reynaud, C., …Carriere, M. (2009). Size-, composition-and shape-dependent toxicological impact of metal oxide nanoparticles and carbon nanotubes toward bacteria. *Environmental science & technology, 43*(21), 8423–8429.

Sperling, R. A., & Parak, W. J. (2010). Surface modification, functionalization and bioconjugation of colloidal inorganic nanoparticles. *Philosophical Transactions of the Royal Society of London A: Mathematical, Physical and Engineering Sciences, 368*(1915), 1333–1383.

Srisitthiratkul, C., Pongsorrarith, V., & Intasanta, N. (2011). The potential use of nanosilver-decorated titanium dioxide nanofibers for toxin decomposition with antimicrobial and self-cleaning properties. *Applied Surface Science, 257*(21), 8850–8856.

Wang, H., Kou, X., Pei, Z., Xiao, J. Q., Shan, X., & Xing, B. (2011). Physiological effects of magnetite (Fe3O4) nanoparticles on perennial ryegrass (*Lolium perenne* L.) and pumpkin (*Cucurbita mixta*) plants. *Nanotoxicology, 5*(1), 30–42.

Xia, T., Kovochich, M., Brant, J., Hotze, M., Sempf, J., Oberley, T., … Nel, A. E. (2006). Comparison of the abilities of ambient and manufactured nanoparticles to induce cellular toxicity according to an oxidative stress paradigm. *Nano Letters, 6*(8), 1794–1807.

Zeyons, O., Thill, A., Chauvat, F., Menguy, N., Cassier-Chauvat, C., Oréar, C., … Spalla, O. (2009). Direct and indirect CeO2 nanoparticles toxicity for *Escherichia coli* and Synechocystis. *Nanotoxicology, 3*(4), 284–295.

Zhang, L. W., William, W. Y., Colvin, V. L., & Monteiro-Riviere, N. A. (2008). Biological interactions of quantum dot nanoparticles in skin and in human epidermal keratinocytes. *Toxicology and Applied Pharmacology, 228*(2), 200–211.

Zhang, L., Pornpattananangkul, D., Hu, C.-M., & Huang, C.-M. (2010). Development of nanoparticles for antimicrobial drug delivery. *Current Medicinal Chemistry, 17*(6), 585–594.

Zhu, L., Chang, D. W., Dai, L., & Hong, Y. (2007). DNA damage induced by multiwalled carbon nanotubes in mouse embryonic stem cells. *Nano Letters, 7*(12), 3592–3597.

Zhu, X., Chang, Y., & Chen, Y. (2010). Toxicity and bioaccumulation of TiO2 nanoparticle aggregates in *Daphnia magna*. *Chemosphere, 78*(3), 209–215.