ejpmr, 2018,5(8), 28-35

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH
www.ejpmr.com

Review Article
ISSN 2394-3211
EJPMR

ANTIMICROBIAL ACTIVITY OF NANOPARTICLES: AN ALTERNATE AGAINST DRUG-RESISTANT PATHOGENIC MICROBES

Ambash Riaz*[1] and Shahid Raza[1]

[1]Dpartment of Biotechnology, University of South Asia, Lahore, Pakistan.

***Corresponding Author: Ambash Riaz**
Dpartment of Biotechnology, University of South Asia, Lahore, Pakistan.

Article Received on 25/05/2018 **Article Revised on 13/06/2018** **Article Accepted on 03/07/2018**

ABSTRACT
Antimicrobial agents, considered as miracle drugs, can be obtained from natural sources such as plant or animal or can be produce synthetically. They are used against various pathogens however, the misuse of these drugs has resulted in the development of drug resistance in pathogenic microbes, which is one of the biggest challenges in healthcare field and is a substantial global threat. Another concern that arises from this, is the spreading of the resistant organism. The alternative of conventional antimicrobial drugs is being studied and research. In the present situation, nanoparticles are considered as new and effective therapeutic agent. The exceptional physiochemical characteristics of nanoparticles with the addition of growth inhibitory capabilities against microorganisms led the increase in nanoparticle studies and their effective antimicrobial applications. In the past, silver was used as therapeutic agent to treats chronic wounds and burns moreover, copper was used for water cleaning. It is much apparent that many of the metallic compounds have antimicrobial characteristic. Present days, the convergence of biology and nanotechnology has taken metal in the form of nanoparticles as an effective agent as many microorganisms. Nanoparticles have unique and well organized chemical and physical characteristics that can be altered according to the situation. In addition to that, potential antimicrobial efficiency because of their large surface area to volume ratio has given them an upper hand over chemical antimicrobial agents which is now having problem of drug resistance in microorganisms.

KEY WORDS: Nanoparticles, antimicrobial, resistant organisms.

INTRODUCTION

Antimicrobial substances inhibit the growth of large range of pathogenic microbs such as fungi, bacteria and viruses. Antimicrobial may be of animal or plants sources or may be synthetic or they may be chemically modified natural substances (Von *et al*, 2006). They are used for various purposes such as chemotherapy and prophylaxis. The mode of action of antimicrobial drugs includes inhibition of synthesis of protein, inhibition of synthesis of cell wall, inhibition or alteration of intermediate metabolism and inhibition of replication of DNA (Awad *et al*, 2010). It is necessary for antimicrobials to penetrate into the cell if their target is present inside the cell of microorganism. Hence, antimicrobial substances must have ability to penetrate into cell to the site of action. However, microbes have shown a remarkable ability of survive, adapt and evolve by developing resistance to antimicrobial substances. The misuse of antimicrobial substances has led to the advancement of new resistant processes in microbes which eventually spread in the microbes globally. This threaten the treatment of even simple infectious diseases. (Gudepalya *et al* 2016)

There are various factors which resulted in the development of antimicrobials resistance in pathogens, these factors include 1) lessen binding capacity of drug because of modification in the binding site, 2) modification or inactivation of the antimicrobial substances 3) decrease in the antimicrobial effect because of the alteration of metabolic pathways or 4) reduced permeability or enhanced active reflex which led to the decrease of intracellular accumulation of antimicrobial substances (Schmieder and Edwards, 2012). However, antimicrobial resistance may be inherent or developed; it can be acquired by developing the mutation in existing genes (Crumplin and Odell, 1987: Martinez and Baquero, 2000) or through the transfer of genes from one microbial specie to another (Palmer and Kos, 2010: Hegstad *et al* 2010).

Resolving antimicrobial resistance is a main priority in human, animal and plant health. Various strategies are analyzed to cope the antimicrobial resistance, these strategies include, minimization of extensive use of antimicrobial agents, collection and study of data, prevention of misuse of antimicrobials agents in animal farms, advancement in development of new drugs and nanotechnology (Laxminarayan *et al*, 2013: Akhtar *et al*, 2015). Emerging nanotechnology have led to the development of organic and inorganic molecules with nano size with efficient industrial applications, textiles, food packaging, therapeutics and healthcare field. The development of new nano-sized antimicrobial substances can be used as an alternative technique to cope the antimicrobial resistance (Akhtar *et al*, 2015). The advancement in nanotechnology, the major leading invention of present time, has modernized healthcare field.

The demand for nan-based products is increasing day by day. The technology has a reflective influence on refining human health. Increased durability, strength, performances, flexibility and unique physical and chemical characteristics of nano substances have been analyzed in the health industry. Nanomaterials can be used in various treatments such as targeted drug delivery, predictive visual monitoring of treatment and for the tumor detection (Wong *et al*, 2013: Jena *et al*, 2013).

Nanoparticles (NPs)

The use of nanoparticles as antimicrobial agents is highly promising and gaining a lot of interest as they might fill the lacking that antibiotics demonstrate which includes coping multidrug resistant microbial strains and biofilms (Zhang *et al*, 2010: Pelgrift and Friedman, 2013). Antimicrobial nanomaterials such as metal, oxides of metal and organic NPs, exhibit a wide range of intrinsic chemical composition characteristics. Hence, it is not surprising that they have various mode of actions. Moreover, the target pathogens vary accordingly to their genetic makeup and eventually in their cell wall structure, important metabolic pathways and various components which if raptured, could be fatal to the microbes. The physiological state of pathogens such as their growth rate, stationary or starved great add to the sensitivity of pathogens to nano material (Baek and An, 2011: Nath and Banerjee, 2013). In some scenarios, the ration between nano material and pathogens is critical to the latter's toxicity (Huh and Kwon, 2011). Furthermore, various environmental factors also contribute and effect the antimicrobial activity of nano materials to pathogens. The physical and chemical characteristics of the NPs such as shape, size, chemical alteration and coating, and mixture of many ratios of other NPs and solvent used, all contribute to effectiveness of NPs regarding their antimicrobial activity (Gatoo *et al*, 2014). Hence, with this complexity, it is no surprising that nano materials antimicrobial mode of action and hazard level they inflict on pathogens are still unclear and one can find contradictory analysis and reports in literature (Ashkarrann 2012: Hajipour *et al*, 2012).

Nonetheless, usually nano materials act along two important fatal pathways which are similar to each other and in various cases occurs concurrently, these pathways are; a) disruption of integrity and potential of membrane, b) release of reactive oxygen species (ROS), also called as oxygen free radicals. (Huh and Kwon, 2011: Blecher *et a*, 2011: Pelgrift and Friedman, 2013).

NPs damage the pathogens' membranes when they bind electrostatically to the pathogens' cell wall and membranes, followed by the modification of membrane, depolarization of membrane, loss of integrity which eventually result in an imbalanced transport, reduced respiration, disruption transduction of energy or cell lysis, and ultimately death of cell (Pelgrift and Friedman, 2013). ROS are considered to be the most effective determinants for both in vivo and in vitro cytotoxicity of NPs and are directly induced because of disruption of respiratory chain or directly by NPs themselves (Nathan and Cunningham-Bussel, 2013). A spurt of ROS causes, through great oxidative stress, damage to all macromolecules of cell, followed by peroxidation of lipids, protein alteration, enzyme inhibitions and damage of DNA and RNA. High dose of ROS causes death of cell and low concentration cause severe damage to DNA and sometime cause mutation (Pan *et al*, 2010: Wang *et al*, 2011). In some scenarios, where ROS produce by UV or visible light (Matˇeejka and Tokarsk´y, 2014), the toxicity of NPs is phtocatalytic. For example, titanium di oxide (TiO2) NPs exhibited induce peroxidation of lipids under UV light which resulted in dysfunction of respiration and death of E. coli cell (Maness *et al*, 1999).

Many other factors of NPs include inhibition of many important enzymes directly, production of nitrogen reactive species (Huh and Kwon, 2011: Blecher *et al*, 2011: Hajipour *et al*, 2012: Pelgrift and Friedman, 2013) and initiation of programmed cell death (Beyth *et al*, 2010).

Inorganic NPs with Antimicrobial Activities

Metals and their oxides have been majorly studied, analyzed and experimented for their antimicrobial activities (Loomba and Scarabelli, 2013). Metal oxides NPs, well known for their lethal antimicrobial effect include titanium oxide (TiO2) NPs, silver (Ag) NPs and zinc oxide (ZnO) NPs. Most NPs of metal oxides show antimicrobial characteristics via reactive oxygen species (ROS) production, while some are effective because of release of metal ion and their physical structure.

Silver Nanoparticle (Ag-NPs)

Among many metal NPs, silver nanoparticles have been commonly used for a potential antimicrobial agent against pathogens such as fungi, bacteria and viruses (Rai *et al*, 2009). Effect of silver nanoparticles was known in ancient times. Silver and its compounds have been used for the medical services, disinfection and purification of water for a long time. In healthcare field, silver compounds are generally applied for the treatment of wounds, burns and many infectious diseases (Elliott, 2010: Aditya *et al*, 2013: Avalos *et al* 2014). The antimicrobial efficiency of silver, compare to other metals and their oxides NPs, was documented to be dependent of size (Poulose *et al*, 2014). Though the action mechanism of silver nanoparticles is still unclear, silver nanoparticles with less diameter have better antimicrobial activity compare to the large diameter silver nanoparticles (Pan´aˇcek, *et al*, 2006). Furthermore, antimicrobial efficiency of Ag-NPs surpasses that of their bulk equivalent. However, high surface energy may conciliate their efficiency because of their vulnerability to combine into large particles, which then may compromise their antimicrobial activity.

Like many other non-antibiotic treatment, silver as antimicrobial agent, was abandoned when penicillin, followed by other antibiotics, were discovered. However, present day with the rise of antibiotics resistance microbial strains, it has regained its new yet controversial status (Chopra, 2007). Silver was stated to be an effective antimicrobial agent against many pathogenic microorganisms I both in vivo and I vitro (de Simone et al, 2014). Furthermore, it is reported that bacteria seem to be less prone to develop resistant against silver compare to other antibiotics (Leid et al, 2012: Chernousova and Epple, 2013). Nevertheless, many controversial debate remain to be solved such as; the debate on the determination of minimal inhibitory concentration (MIC) of silver and its breaking point, the ease of advent of resistant strains (Silver, 2003: Ugur and Ceylan, 2003), whether silver NPs kill only biofilms or just planktonic cells (Sheng and Liu, 2011), or side effects of silver NPs on human health humans (Drake and Hazelwood, 2005: Tolaymat et al, 2010: Bartłomiejczyk et al, 2013). Furthermore, the antimicrobial mechanisms of Ag-NPs are not completely understood (Majdalawieh et al, 2014). It is reported that in Gram-negative Bacteria E. coli, Ag-NPs caused pits in the cell wall by enhancing the permeability of membrane and by deactivating the respiratory chain (Sondi and B. Salopek-Sondi, 2004: Beyth et al, 2010). Other studies demonstrated that the silver ions, which has an affinity to nitrogen and sulfur, can deter and disturb structure of protein by binding with amino and thiol group (Choi et al, 2008). In conclusion, it was determined that the Ag-NPs are photocatalytic (Ashok et al, 2014) and can initiate ROS (Carlson et al, 2008: Piao et al, 2011: Ninganagouda et al, 2014), an analysis that was controversial by others demonstrated that, in eukaryotic cells, this effect is dependent of the type of cell (Luther et al, 2011: Greulich et al, 2011). It is also reported that Ag-NPs demonstrated to have synergistic antimicrobial effect on both Gram-negative and Gram-positive bacteria when applied in combination with different antibiotics (Shahverdi et al, 2007: Khurana et al, 2014). Nevertheless, regardless the controversial debates, Ag-NPs are probably the most promising method against resistant pathogens.

Titanium Oxide Nanoparticles (TiO2-NPs)

Similar to Ag-NPs, titanium dioxide nanoparticles (TiO2-NPs) has been extensively studied and experimented for its antimicrobial effect (Allahverdiyev et al, 2011). TiO2 has been known for its capability to kill both Gram-negative and Gram-positive bacteria (Wei et al, 1994). Currents studies has demonstrated the efficiency of TiO2 against many parasite and viral species (Zan et al, 2007: Brady-Est´evez et al, 2008: Allahverdiyev et al, 2013).

TiO2-NPs as antimicrobial agents have been commercialized for quite some time (Maness et al, 1999). Similar to silver, TiO2-NPs are photocatalytic; their toxicity is induced by UV or visible light (Pelgrift and Friedman, 2013), influenced ROS spurt. The ROS disrupt the cell membrane, DNA and various other macromolecules and ultimately the function of microbial cell (Blecher et al, 2011). TiO2-NPs are efficient against many bacterial strains including Bacillus spores (Hamal et al, 2010), which is most antibiotic resitant organism known. Combination of Ti or its oxide with other NPs, such as silver, demonstrated synergistic effect and increase their antimicrobial activity (Pratap et al, 2007: Devi and Nagaraj, 2014: Ungureanu et al, 2014).

Zinc Oxide Nanoparticle (ZnO-NPs)

Another broad spectrum antimicrobial NPs are ZnO-NPs (Palanikumar et al, 2014). ZnO-NPs demonstrated to have a broad range of antimicrobial effect against many different kind of microbes, which is greatly dependent on the certain dose and size of particles (Palanikumar et al, 2014). Furthermore, ZnO-NPs inhibited the growth of methicillin-resistant S. epidermidis (MRSE), methicillin-resistant S. aureus (MRSA), and methicillin-sensitive S. aureus (MSSA) strains and proved to be efficient antimicrobial agents that were ineffective by the resistant process of MRSE and MRSA (Ansari et al, 2012: Malka et al, 2013).

ZnO-NPs are relatively cheap (Huh and Kwon, 2011) and effective (Palanikumar et al, 2014) against broad range of pathogenic microbes (Huang et al, 2008: Hakraborti et al, 2014). These pathogenic microbes include; Salmonella enteritidis, Listeria monocytogenes (Jin et al, 2009), E. coli (Jin et al, 2009: Liu et al, 2009), Klebsiella pneumonia (Reddy et al, 2014), Lactobacillus and Streptococcus mutans, (Kasraei et al, 2014) with low toxicity to human cells (Reddy et al, 2007). The white color of ZnO-NPs blocks UV light and have capability to prevent formation of biofilms which make them appropriate for glass (Applerot et al, 2012) and fabric (Dastjerdi and Montazer, 2010) industries as coating ingredient designed for medical and other devices. Moreover, FDA approved zinc based treatment and current Zn is used for food additive (Blecher et al, 2011).

Antimicrobial activity of organic nanoparticles

Polymeric/organic NPs kill microbes either by releasing antimicrobial peptides, antibiotics, antimicrobial substances or direct contact with cationic surfaces such as alkyl pyridiniums, quaternary phosphonium and quaternary ammonium compounds. Many mechanism action have been analyzed for how these cationic groups raptured the cell membrane of microbes, to allow the penetration of hydrophobic polymeric chain into the cell and disrupt the membrane. It has been analyzed that enhance level of positive charge have ability to confer antimicrobial characteristics regardless of hydrophobic chain length, possibly through an ion exchange process between the charged surface and cell membrane of pathogens. The antimicrobial ability of polycations is dependent on the capability of charges to attach and interact with the plasma membrane. The experiments propose that the engineering wide range of positively charged polymer surfaces can create a variety of contact killing materials (Lichter and Rubner, 2009).

Organic antimicrobial substances are considered less stable in nature especially in high temperature compare to inorganic substances. This may result in complications which arise when designing product supposed to be stable and can cope the harsh conditions of processing. Hence, inorganic NPs material are more often used against pathogenic microbes as compare to organic nano-size materials (Nurit *et al*, 2015).

Quaternary Ammonium Compounds

Quaternary ammonium compounds (QAC) such as benzalkonium chloride, stearalkonium chloride and cetrimonium chloride are considered to be well known disinfectants. The length of N-alkyl chain regulates the antimicrobial activity of QACs. QACs with alkyl chain length of 12-114 carbons have effective antimicrobial activity against gram positive bacteria, while QACs with 14-16 carbon are effective against gram negative bacteria (Xue *et al*, 2015). The mode of action of QACs is based on the interaction of positively charge QACs and negatively charged bacterial membrane. QACs denature the structural protein and enzymes of microbes by integration of QAC hydrophobic tail into the hydrophobic membrane. Nano-sized substances integrated with N-alkylated polyethyleneimine (PEI) have antimicrobial activity against fungal strains with most antibiotic resistance efficiency, gram-negative and gram-positive bacteria, both airborne and water, by rupturing the cell membrane (Beyth *et al*, 2015). Replacement of PEIs with different group also has antimicrobial activity of C. albicans. Au-NPs and TiO2 have shown an excellent antimicrobial activity without external excitation (Wan and Yeow, 2012). It is analyzed that quaternary ammonium compounds integrated with Si-NPs have shown an 96.6% antimicrobial activity against *E. coli*, 98.5% against *S. aureus* and 99.6% *Deinococcus geothermalis* compared to Si-NPs alone (Song *et al*, 2011). Similarly, NPs based on QAC-PEI completely repressed the growth of *E. coli* and *S. aureus* (Yudovin-Farber *et al*, 2010).

Polysiloxanes

Another major class of organic NPs is polysiloxanes, of silicon oxide (SiO2). Block and statistical siloxane copolymer with quaternary ammonium salt exhibited great antimicrobial activity against both *Staphylococcus aureus* and *E. coli* (sauvet *et al*). however, no difference was analyzed in both statistical copolymer and block type polymers (Sauvet *et al*, 2003).

Triclosan

Triclosan is amongst the most widely used antimicrobial agent. A study experimented the effect of solution of water-based styrene-acrylate emulsion with tricolsan against Ent*erococcus faecalis*. According to agar diffusion test, it was shown that the triclosan release depends on the solvent, almost very slow or totally repressed with water and very fast with n-heptane (Chung *et al*, 2003). Triclosan with water-PVA nanoparticles exhibits the effective antimicrobial activity against Corynebacterium compare to organic solution of triclosan (Zhang *et al*, 2008).

Chitosan

Chitosan NPs show a wide range of antimicrobial activity against fungi, bacteria and viruses. The characteristics properties of chitosan such as, non-toxicity, bio-compatibility, antimicrobial activity, low immunogenicity, and its ability of increase absorption, enhances its usage in many fields (Beyth *et al*, 2015: Cheung *et al*, 2015). The antimicrobial activity of chitosan-NPs depends on many factors such as solvent and pH (Beyth *et al*, 2015). The NPs shows efficient antifungal activity against *Fusarium solani* and *C. albicans.* However, some fungal strains such as *A. niger* exhibit resistance to the NPs. The zeta potential is assumed to have an influence on the negatively charged surface of microbes and add to the antifungal activity of chitosan (Yien *et al*, 2012).

CONCLUSIONS

The emergence of drug resistant microbes carried a great challenge in healthcare field. Microbes create antimicrobial resistance by many mechanisms. Medicines based on nanotechnology offer the chance of early detection, NP based bio-imaging and treatment of diseases caused by drug resistant microbes. The advances in the development or synthesis of NPs has also greatly developed the biomedicine field. Many NPs have been synthesized by different research studies and their antimicrobial effect has been experimented on various microbes. The synthesis of NPs using biological techniques decreases the environmental concerns related to their chemical synthesis. Many research experiments have created biological methods for the NPs synthesis which are environmental friendly. The mode of action of NPs differ with the NP type, their composition and size. NPs have wide range of application in various other fields beside health department such as cancer therapy, gene and drug delivery and bio-imaging.

REFERENCES

1. Aditya N. P., P. G. Vathsala, V. Vieira, R. S. R. Murthy, and E. B. Souto, "Advances in nanomedicines for malaria treatment," Advances in Colloid and Interface Science, 2013; 201-202: 1–17.
2. Akhtar, M.; Swamy, M.K.; Umar, A.; Sahli, A.; Abdullah, A. Biosynthesis and characterization of silver nanoparticles from methanol leaf extract of Cassia didymobotyra and assessment of their antioxidant and antibacterial activities. J. Nanosci. Nanotechnol. 2015; 15: 9818–9823.
3. Allahverdiyev A. M., E. S. Abamor, M. Bagirova *et al*., "Investigation of antileishmanial activities of Tio2@Ag nanoparticles on biological properties of L. tropica and L. infantum parasites, in vitro," Experimental Parasitology, 2013; 135(1): 55–63.
4. Allahverdiyev A. M., E. S. Abamor, M. Bagirova, and M. Rafailovich, "Antimicrobial effects of TiO2 and Ag2O nanoparticles against drug-resistant bacteria and leishmania parasites," Future Microbiology, 2011; 6(8): 933–940.
5. and Escherichia coli," Nanomedicine: Nanotechnology, Biology, and Medicine, 2007; 3(2): 168–171.
6. and Technology, 2003; 38(2): 165–169.
7. Ansari M. A., H. M. Khan, A. A. Khan, A. Sultan, and A. Azam, "Characterization of clinical strains of MSSA, MRSA andMRSE isolated from skin and soft tissue infections and the antibacterial activity of ZnO nanoparticles," World Journal of Microbiology&Biotechnology, 2012; 28(4): 1605–1613.
8. apoptosis," Toxicology Letters, 2011; 201(1): 92–100.
9. Applerot G., J. Lellouche, N. Perkas, Y. Nitzan, A. Gedanken, and E. Banin, "ZnO nanoparticle-coated surfaces inhibit bacterial biofilm formation and increase antibiotic susceptibility," RSC Advances, 2012; 2(6): 2314–2321.
10. Ashkarran A. A., M. Ghavami, H. Aghaverdi, P. Stroeve, andM. Mahmoudi, "Bacterial effects and protein corona evaluations: crucial ignored factors in the prediction of bio-efficacy of
11. Ashok D. Kumar,V. Palanichamy, and S. M. Roopan, "Photocatalytic action ofAgCl nanoparticles and its antibacterial activity," Journal of Photochemistry and Photobiology B: Biology, 2014; 138: 302–306.
12. Avalos A., A. I. Haza, D.Mateo, and P.Morales, "Interactions of manufactured silver nanoparticles of different sizes with normal human dermal fibroblasts," InternationalWound Journal, 2014.
13. Awad, H.M.; Kamal, Y.E.S.; Aziz, R.; Sarmidi, M.R.; El-Enshasy, H.A. Antibiotics as microbial secondary metabolites: Production and application. J. Teknol. 2012; 59: 101–111.
14. Baek Y.-W. and Y.-J. An, "Microbial toxicity of metal oxide nanoparticles (CuO, NiO, ZnO, and Sb2O3) to Escherichia coli, Bacillus subtilis, and Streptococcus aureus," The Science of the Total Environment, 2011; 409(8): 1603–1608.
15. Bartłomiejczyk T., A. Lankoff, M. Kruszewski, and I. Szumiel, "Silver nanoparticles—allies or adversaries?" Annals of Agricultural and EnvironmentalMedicine, 2013; 20(1): 48–54.
16. Beyth N., I. Yudovin-Farber, M. Perez-Davidi, A. J. Domb, and E. I.Weiss, "Polyethyleneimine nanoparticles incorporated into resin composite cause cell death and trigger biofilm stress in vivo," Proceedings of the National Academy of Sciences of the United States of America, 2010; 107(51): 22038–22043.
17. Beyth, N.; Houri-Haddad, Y.; Domb, A.; Khan, W.; Hazan, R. Alternative antimicrobial approach: Nano-antimicrobial materials. Evid. Based Complement. Altern. Med. 2015, 2015.
18. Blecher K., A. Nasir, and A. Friedman, "The growing role of nanotechnology in combating infectious disease," Virulence, 2011; 2(5): 395–401.
19. Brady-Est´evez A. S., S. Kang, and M. Elimelech, "A singlewalled- carbon-nanotube filter for removal of viral and bacterial pathogens," Small, 2008; 4(4): 481–484.
20. Carlson C., S. M.Hussein, A. M. Schrand *et al*., "Unique cellular interaction of silver nanoparticles: size-dependent generation of reactive oxygen species," Journal of Physical Chemistry B, 2008; 112(43): 13608–13619.
21. Chernousova S. and M. Epple, "Silver as antibacterial agent: ion, nanoparticle, and metal," Angewandte Chemie—International Edition, 2013; 52(6): 1636–1653.
22. Cheung, R.C.F.; Ng, T.B.; Wong, J.H.; Chan, W.Y. Chitosan: An update on potential biomedical and pharmaceutical applications. Mar. Drugs. 2015; 13: 5156–5186.
23. Choi O., K. K. Deng, N.-J. Kim, L. Ross Jr., R. Y. Surampalli, and Z. Hu, "The inhibitory effects of silver nanoparticles, silver ions, and silver chloride colloids on microbial growth," Water Research, 2008; 42(12): 3066–3074.
24. Chopra I., "The increasing use of silver-based products as antimicrobial agents: a useful development or a cause for concern?" The Journal of Antimicrobial Chemotherapy, 2007; 59(4): 587–590.
25. Chung D., S. E. Papadakis, and K. L. Yam, "Evaluation of a polymer coating containing triclosan as the antimicrobial layer for packaging materials," International Journal of Food Science
26. Crumplin, G.C.; Odell, M. Development of resistance to ofloxacin. Drugs 1987; 34: 1–8.
27. Dastjerdi R. and M. Montazer, "A review on the application of inorganic nano-structured materials in the modification of textiles: focus on anti-microbial properties," Colloids and Surfaces B: Biointerfaces, 2010; 79(1): 5–18.
28. De Simone S., A. L. Gallo, F. Paladini, A. Sannino, and M. Pollini, "Development of silver nano-coatings on silk sutures as a novel approach against

surgical infections," Journal of Materials Science:Materials inMedicine, 2014; 25(9): 2205–2214.
29. Devi L. G. and B.Nagaraj, "Disinfection of Escherichia coli gram negative bacteria using surface modified TiO2: optimization of Ag metallization and depiction of charge transfer mechanism," Photochemistry and Photobiology, 2014; 90(5): 1089–1098.
30. Drake P. L. and K. J. Hazelwood, "Exposure-related health effects of silver and silver compounds: a review," The Annals of Occupational Hygiene, 2005; 49(7): 575–585.
31. Elliott C., "The effects of silver dressings on hronic and burns wound healing," British Journal of Nursing, 2010; 19(15): S32–S36.
32. Future Microbiol. 2012; 7: 73–89.
33. Gatoo M.A., S.Naseem, M. Y. Arfat, A. M. Dar, K. Qasim, and S. Zubair, "Physicochemical properties of nanomaterials: implication in associated toxic manifestations," BioMed Research International, vol. 2014, Article ID 498420, 8 pages, 2014.
34. Greulich C., J. Diendorf, J. Gessmann *et al*., "Cell type-specific responses of peripheral blood mononuclear cells to silver nanoparticles," Acta Biomaterialia, 2011; 7(9): 3505–3514.
35. Gudepalya Renukaiah Rudramurthy, Mallappa Kumara Swamy 2, Uma Rani Sinniah 2 and Ali Ghasemzadeh Nanoparticles: Alternatives Against Drug-Resistant Pathogenic Microbes. Molecules 2016; 21: 836.
36. Hajipour M. J., K. M. Fromm, A. A. Ashkarran *et al*., "Antibacterial properties of nanoparticles," Trends in Biotechnology, 2012; 30(10): 499–511.
37. Hakraborti S., A. K.Mandal, S. Sarwar, P. Singh, R. Chakraborty, and P. Chakrabarti, "Bactericidal effect of polyethyleneimine capped ZnO nanoparticles on multiple antibiotic resistant bacteria harboring genes of high-pathogenicity island," Colloids and Surfaces B: Biointerfaces, 2014; 121C: 44–53.
38. Hamal D. B., J. A. Haggstrom, G. L. Marchin, M. A. Ikenberry, K. Hohn, and K. J. Klabunde, "A multifunctional biocide/ sporocide and photocatalyst based on titanium dioxide (TiO2) codoped with silver, carbon, and sulfur," Langmuir, 2010; 26(4): 2805–2810.
39. Hegstad, K.; Mikalsen, T.; Coque, T.M.; Werner, G.; Sundsfjord, A. Mobile genetic elements and their contribution to the emergence of antimicrobial resistant Enterococcus faecalis and Enterococcus faecium. Clin. Microbiol. Infect. 2010; 16: 541–554.
40. Huang Z., X. Zheng, D. Yan *et al*., "Toxicological effect of ZnO nanoparticles based on bacteria," Langmuir, 2008; 24(8): 4140–4144.
41. Huh A. J. and Y. J. Kwon, "'Nanoantibiotics': a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era," Journal of Controlled Release, 2011; 156(2): 128–145.
42. Jena, M.; Mishra, S.; Jena, S.; Mishra, S.S. Nanotechnology-future prospect in recent medicine: A review. Int. J. Basic Clin. Pharmacol. 2013; 2: 353–359.
43. Jin T., D. Sun, J. Y. Su, H. Zhang, and H.-J. Sue, "Antimicrobial efficacy of zinc oxide quantum dots against Listeria monocytogenes, Salmonella Enteritidis, and Escherichia coli O157:H7," Journal of Food Science, 2009; 74(1): M46–M52.
44. Kasraei S., L. Sami, S. Hendi, M.-Y. AliKhani, L. Rezaei- Soufi, and Z. Khamverdi, "Antibacterial properties of composite resins incorporating silver and zinc oxide nanoparticles on
45. Khurana C., A. K. Vala, N. Andhariya, O. P. Pandey, and B. Chudasama, "Antibacterial activities of silver nanoparticles and antibiotic-adsorbed silver nanoparticles against biorecycling microbes," Environmental Science: Processes & Impacts, 2014; 16(9): 2191–2198.
46. Laxminarayan, R.; Duse, A.;Wattal, C.; Zaidi, A.K.;Wertheim, H.F.; Sumpradit, N.; Vlieghe, E.; Hara, G.L.; Gould, I.M.; Goossens, H.; Greko, C. Antibiotic resistance—The need for global solutions. Lancet Infect. Dis. 2013; 13: 1057–1098.
47. Leid J. G., A. J. Ditto, A. Knapp *et al*., "In vitro antimicrobial studies of silver carbene complexes: activity of free and nanoparticle carbene formulations against clinical isolates of pathogenic bacteria," The Journal of Antimicrobial Chemotherapy, 2012; 67(1): 138–148.
48. Lichter J. A. andM. F. Rubner, "Polyelectrolyte multilayers with intrinsic antimicrobial functionality: the importance of mobile polycations," Langmuir, 2009; 25(13): 7686–7694.
49. Liu Y., L. He, A. Mustapha, H. Li, Z. Q. Hu, and M. Lin, "Antibacterial activities of zinc oxide nanoparticles against Escherichia coli O157:H7," Journal of Applied Microbiology, 2009; 107(4): 1193–1201.
50. Loomba L. and T. Scarabelli, "Metallic nanoparticles and their medicinal potential. Part I. Gold and silver colloids," Therapeutic Delivery, 2013; 4(7): 859–873.
51. Luther E. M., Y. Koehler, J. Diendorf, M. Epple, and R. Dringen, "Accumulation of silver nanoparticles by cultured primary brain astrocytes," Nanotechnology, vol. 22, no. 37, Article ID 375101, 2011.
52. Majdalawieh A., M. C. Kanan, O. El-Kadri, and S. M. Kanan, "Recent advances in gold and silver nanoparticles: synthesis and applications," Journal of Nanoscience and Nanotechnology, 2014; 14(7): 4757–4780.
53. Malka E., I. Perelshtein, A. Lipovsky *et al*., "Eradication ofmultidrug resistant bacteria by a novel Zn-doped CuO nanocomposite," Small, 2013; 9(23): 4069–4076.
54. Maness P.-C., S. Smolinski, D. M. Blake, Z. Huang, E. J. Wolfrum, and W. A. Jacoby, "Bactericidal activity of photocatalytic TiO2 reaction: toward an

understanding of its killing mechanism," Applied and Environmental Microbiology, 1999; 65(9): 4094–4098.
55. Martinez, J.L.; Baquero, F. Mutation frequencies and antibiotic resistance. Antimicrob. Agents Chemother. 2000; 44: 1771–1777.
56. Matˇeejka V. and J. Tokarsk´y, "Photocatalytical nanocomposites: a review," Journal of Nanoscience and Nanotechnology, 2014; 14(2): 1597–1616.
57. Nath D. and P. Banerjee, "Green nanotechnology—a new hope for medical biology," Environmental Toxicology and Pharmacology, 2013; 36(3): 997–1014.
58. Nathan C. and A. Cunningham-Bussel, "Beyond oxidative stress: an immunologist's guide to reactive oxygen species," Nature Reviews Immunology, 2013; 13(5): 349–361.
59. Ninganagouda S., V. Rathod, D. Singh *et al*., "Growth kinetics and mechanistic action of reactive oxygen species released by silver nanoparticles from Aspergillus niger on Escherichia coli," BioMed Research International, vol. 2014, Article ID 753419, 9 pages, 2014.
60. Nurit Beyth, Yael Houri-Haddad, Avi Domb, Wahid Khan, and Ronen Hazan. Alternative Antimicrobial Approach: Nano-Antimicrobial Materials. Evidence-Based Complementary and Alternative Medicine. 2015: 16.
61. Palanikumar L., S. N. Ramasamy, and C. Balachandran, "Sizedependent antimicrobial response of zinc oxide nanoparticles," IET Nanobiotechnology, 2014; 8(2): 111–117.
62. Palmer, K.L.; Kos, V.N.; Gilmore, M.S. Horizontal gene transfer and the genomics of enterococcal antibiotic resistance. Curr. Opin. Microbiol. 2010; 13: 632–639.
63. Pan X., J. E. Redding, P. A.Wiley, L.Wen, J. S.McConnell, and B. Zhang, "Mutagenicity evaluation of metal oxide nanoparticles by the bacterial reverse mutation assay," Chemosphere, 2010; 79(1): 113–116.
64. Pan´a˘cek A., L. Kv´ıtek, R. Prucek *et al*., "Silver colloid nanoparticles: synthesis, characterization, and their antibacterial activity," The Journal of Physical Chemistry B, 2006; 110(33): 16248–16253.
65. Pati R., R. K. Mehta, S. Mohanty *et al*., "Topical application of zinc oxide nanoparticles reduces bacterial skin infection in mice and exhibits antibacterial activity by inducing oxidative stress response and cell membrane disintegration in macrophages," Nanomedicine: Nanotechnology, Biology, and Medicine, 2014; 10(6): 1195–1208.
66. Pelgrift R. Y. and A. J. Friedman, "Nanotechnology as a therapeutic tool to combat microbial resistance," Advanced Drug Delivery Reviews, 2013; 65(13-14): 1803–1815.
67. Phosphonium Salts. Int. J. Mol. Sci. 2015; 16: 3626–3655.
68. Piao M. J., K. A. Kang, I. K. Lee *et al*., "Silver nanoparticles induce oxidative cell damage in human liver cells through inhibition of reduced glutathione and induction of mitochondriainvolved
69. Poulose S., T. Panda, P. P. Nair, and T. Th´eodore, "Biosynthesis of silver nanoparticles," Journal of Nanoscience and Nanotechnology, 2014; 14(2): 2038–2049.
70. Pratap Reddy M., A. Venugopal, and M. Subrahmanyam, "Hydroxyapatite-supported Ag-TiO2 as Escherichia coli disinfection photocatalyst," Water Research, 2007; 41(2): 379– 386.
71. Rai M., A. Yadav, and A. Gade, "Silver nanoparticles as a new generation of antimicrobials," Biotechnology Advances, 2009; 27(1): 76–83.
72. Reddy K. M., K. Feris, J. Bell, D. G. Wingett, C. Hanley, and A. Punnoose, "Selective toxicity of zinc oxide nanoparticles to prokaryotic and eukaryotic systems," Applied Physics Letters, 2007; 90(21): Article ID 213902.
73. Reddy L. S., M. M.Nisha, M. Joice, and P.N. Shilpa, "Antimicrobial activity of zinc oxide (ZnO) nanoparticle against Klebsiella pneumoniae," Pharmaceutical Biology, 2014; 52(11): 1388– 1397.
74. Sauvet G., W. Fortuniak, K. Kazmierski, and J. Chojnowski, "Amphiphilic block and statistical siloxane copolymers with antimicrobial activity," Journal of Polymer Science Part A: Polymer Chemistry, 2003; 41(19): 2939–2948.
75. Schmieder, R.; Edwards, R. Insights into antibiotic resistance through metagenomic approaches.
76. Shahverdi A. R., A. Fakhimi, H. R. Shahverdi, and S. Minaian, "Synthesis and effect of silver nanoparticles on the antibacterial activity of different antibiotics against Staphylococcus aureus
77. Sheng Z. and Y. Liu, "Effects of silver nanoparticles on wastewater biofilms," Water Research, 2011; 45(18): 6039–6050.
78. Silver S., "Bacterial silver resistance: molecular biology and uses and misuses of silver compounds," FEMSMicrobiology Reviews, 2003; 27(2-3): 341–353.
79. Sondi I. and B. Salopek-Sondi, "Silver nanoparticles as antimicrobial agent: a case study on E. coli as a model for Gramnegative bacteria," Journal of Colloid and Interface Science, 2004; 275(1): 177–182.
80. Song, J.; Kong, H.; Jang, J. Bacterial adhesion inhibition of the quaternary ammonium functionalized silica nanoparticles. Coll. Surf. B 2011; 82: 651–656.
81. Streptococcusmutans and Lactobacillus," RestorativeDentistry& Endodontics, 2014; 39(2): 109–114.
82. Tolaymat, A.M. El Badawy, A. Genaidy, K. G. Scheckel, T. P. Luxton, and M. Suidan, "An evidence T. M. -based environmental perspective of manufactured silver nanoparticle in syntheses and applications: a systematic review and critical

appraisal of peer-reviewed scientific papers," Science of the Total Environment, 2010; 408(5): 999–1006.
83. Ugur A. and ¨ O. Ceylan, "Occurrence of resistance to antibiotics, metals, and plasmids in clinical strains of Staphylococcus spp.," Archives of Medical Research, 2003; 34(2): 130–136.
84. Ungureanu C., S. Popescu, G. Purcel *et al*., "Improved antibacterial behavior of titanium surface with torularhodin-polypyrrole film,"Materials Science&Engineering C:Materials for Biological Applications, 2014; 42: 726–733.
85. various forms of silver nanoparticles," Chemical Research in Toxicology, 2012; 25(6): 1231–1242.
86. Von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Habich, D. Antibacterial natural products in medicinal chemistry—Exodus or revival? Angew. Chem. Int. Ed. **2006;** 45: 5072–5129.
87. Wan,W.; Yeow, J.T. Antibacterial properties of poly (quaternary ammonium) modified gold and titanium dioxide nanoparticles. J. Nanosci. Nnotechnol. 2012; 12: 4601–4606.
88. Wang S., R. Lawson, P. C. Ray, and H. Yu, "Toxic effects of gold nanoparticles on Salmonella typhimurium bacteria," Toxicology and Industrial Health, 2011; 27(6): 547–554.
89. Wei C., W.-Y. Lin, Z. Zalnal *et al*., "Bactericidal activity of TiO2 photocatalyst in aqueous media: toward a solar-assisted water disinfection system," Environmental Science and Technology, vol. 28, no. 5, pp. 934–938, 1994.
90. Wong, I.Y.; Bhatia, S.N.; Toner, M. Nanotechnology: Emerging tools for biology and medicine. Genes Dev. 2013; 27: 2397–2408.
91. Xue, Y.; Xiao, H.; Zhang, Y. Antimicrobial Polymeric Materials with Quaternary Ammonium and
92. Yien, L.; Zin, N.M.; Sarwar, A.; Katas, H. Antifungal activity of chitosan nanoparticles and correlation with their physical properties. Int. J. Biomater. 2012, 2012.
93. Yudovin-Farber, I.; Golenser, J.; Beyth, N.;Weiss, E.I.; Domb, A.J. Quaternary ammonium polyethyleneimine: Antibacterial activity. J. Nanomater. 2010, 2010.
94. Zan L., W. Fa, T. Peng, and Z.-K. Gong, "Photocatalysis effect of nanometer TiO2 and TiO2-coated ceramic plate on Hepatitis B virus," Journal of Photochemistry and Photobiology B: Biology, 2007; 86(2): 165–169.
95. Zhang H., D. Wang, R. Butler *et al*., "Formation and enhanced biocidal activity of water-dispersable organic nanoparticles," Nature Nanotechnology, 2008; 3(8): 506–511.
96. Zhang L., D. Pornpattananangkul, C.-M. J. Hu, and C.-M. Huang, "Development of nanoparticles for antimicrobial drug delivery," Current Medicinal Chemistry, 2010; 17(6): 585– 594.