



Nanotechnology as an Effective Tool for Antimicrobial Applications: Current Research and Challenges

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The prevention and treatment of bacterial infections is a matter of great concern. The high use of antimicrobials/antibiotics for treating bacterial infections in recent years also poses a great risk of developing resistance in many bacterial species. It was also reported that biofilm formation by bacteria prevents the entry of antibiotics and also helps bacteria to develop resistance against any applied antibiotic, making the treatment more difficult. All the current approaches have shown inadequacy to overcome the challenges presented by pathogenic microbes. Therefore, adoption of a better method/strategy to face these challenges is the need of the hour. As per reports, nanotechnology has shown tremendous success in many fields. Moreover, in the last few years, the research highlighted the potential of nanotechnology as an effective tool for antimicrobial applications. Metallic nanoparticles and their oxides such as silver (AgNPs), zinc (ZnAgNPs), gold (AuNPs), iron (FeNPs), copper (CuNPs), titanium (TiNPs), zinc oxide (ZnO-NPs), magnesium oxide (MgO), titanium dioxide (TiO₂-NPs), copper oxides (CuO-NPs) and iron oxides (Fe₂O₃-NPs) are considered effective nano-materials against pathogenic microbes. It was observed that the higher surface area to volume ratio of nanoparticles, the way they interact with bacterial membranes/cell wall and their various antimicrobial mechanisms surpass all the barriers and reach targeted sites,

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thereby making them potential candidate for antimicrobial applications. There is no doubt that nanotechnological strategies/interventions in healthcare sector will revolutionize the current treatment regime. The present review provides the understanding of variety of nanoparticles and their mechanisms for antimicrobial and antibiofilm efficacy, further their role to overcome antibiotic resistance is also highlighted in detail.

Keywords: Antimicrobials; antibiofilm; antibiotic resistance; treatment; nanoparticles.

1. INTRODUCTION

Nanotechnology involves the synthesis and controlled manipulation of very small particles (1-100 nm), which can be used further for various applications. With recent developments, nanotechnology has emerged as a potential agent to control and combat various complications associated with bacterial infections. Many studies have investigated the antibacterial efficacies of different metal/metal oxide nanoparticles, it has been suggested that the metals i.e., silver, zinc, copper etc., possess antibacterial properties in bulk form, however their efficiency increased many folds in its nano form, highlighting the importance of nanostructures [1]. Different nanoparticles can offer different antimicrobial mechanisms and therefore difference in bactericidal activity was observed. However, physical interaction of nanoparticles and release of antibacterial ions from nanoparticle surfaces have been identified for difference in antibacterial efficacy [1-2]. The metal/metal oxide nanoparticles have been widely reported for range of antibacterial efficacies [3-8]. Even low doses of nanoparticles can effectively control bacterial growth. Moreover, silver nanoparticles were found to show lowest cytotoxicity on human cells [9].

The positive charge on nanoparticle helps in the efficient binding with the bacterial membrane. Further, nanoparticles can target various biomolecules and affect different sites of bacterial cell. Nanoparticles can affect the process of biofilm formation, deplete ATPs, and generate ROS leading to protein, enzyme and DNA damage [1,10]. The antibiofilm activity was found to be efficient with small sized nanoparticles (~ 15 nm), as they can easily interact and penetrate the EPS and water channels [11]. Moreover, Lahiri et al. [12] and Samanta et al. [13] highlighted that metal/metal oxide nanoparticles can inhibit the quorum sensing pathway, which affects the formation of biofilm.

Antimicrobial resistance occur when microorganisms started to develop mechanisms to protect themselves from applied antimicrobial

agent. However, the latest challenge of antibiotic resistance among many bacterial species can also overcome by the use of nanotechnological strategies. Nanoparticles naturally possess multi-targeted antimicrobial action, thereby developing resistance for nanoparticles can be very difficult. Studies have highlighted that nanoparticles of silver, copper, zinc oxide, titanium dioxide etc., can effectively control multi-drug resistant bacteria [14-17]. Further, the antibiotic and nanoparticle combination has also reported for synergistic effects of multifold [6], by decreasing the doses of antibiotics.

2. NANOTECHNOLOGY VS. MICROBES

Various metallic/non-metallic nanoparticles are reported for efficient antimicrobial activity. Nanoparticles like iron, silver, copper, gold, copper oxide (CuO), titanium dioxide (TiO₂), magnesium oxide (MgO), zinc oxide (ZnO) etc are found to be effective antibacterial agent (Table 1). Silver possesses natural antibacterial property which increase in its nano-form [18-19]. *Gloeophyllum striatum* synthesized silver nanoparticles showed efficient antimicrobial activity against gram-positive and gram-negative bacteria. The study highlighted that gram-positive bacteria were less susceptible to AgNPs than gram-negative bacteria [20]. Similarly, Jassim et al. [21] highlighted that *Carica papaya* synthesized AgNPs (average diameter of 75.68 nm) found to be effective against *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginos* and *Staphylococcus aureus*. It was also observed that triangular silver nanoparticles are strong biocidal agent than spherical shaped nanoparticles [8,22]. Also, green synthesized gold nanoparticles (spherical shape) using seed extract of *Elettaria cardamomum* exhibited efficient antibacterial activity against pathogenic bacterial strains of *E. coli*, *S. aureus* and *P. aeruginosa*. As per Amer and Awwad [3], green synthesized Cu-NPs acts as an active antimicrobial agent against *E. coli* and *S. aureus*. Recently, Tyagi et al [6] developed zinc oxide nanoparticles through chemical method. The study highlighted efficient antibacterial activity of

zinc oxide nanoparticles against *E. coli* and *Streptococcus* sp. Further, it was also confirmed that there was 2.9 fold increase in antibacterial efficiency when nanoparticle-ciprofloxacin conjugates were used against *E. coli* and *Streptococcus spp.* in comparison to ciprofloxacin alone. The green synthesized spherical copper oxide nanoparticles (5- 10 nm) using the extract of *Gloriosa superba* was found to be effective antibacterial agent against *S. aureus*, *Pseudomonas desmolyticum*, *E. coli*, and *Klebsiella aerogenes* [23]. Further, Caroling et al [24] also reported the antibacterial activity of spherical copper nanoparticles (65 -184 nm) developed using *Phyllanthus embilica* extract. *Azadirachta* leaf synthesized Titanium dioxide nanoparticles (TiO₂NPs) have also displayed effective antibacterial activity against *Salmonella* Typhimurium, *E. coli*, *K. pneumonia* and, *Bacillus subtilis* [7].

2.1 Antimicrobial Mechanism of Nanoparticles

Literature studies have provided various antimicrobial mechanisms of metallic/ non-metallic nanoparticles [6,7,13,19]. It has been highlighted that nanoparticles can interact with membrane, hinders biofilm formation, ATP depletion, ROS generation, which further leads to protein, enzyme and DNA damage, causing bacterial cell death (Figure 1) [1,10]. Studies have also showed the difference in the efficacy of metallic nanoparticles in gram positive and negative bacteria [5,8]. Reports have pointed that the difference in the cell all composition in gram positive and negative bacteria may be responsible for different antibacterial effects. In the case of gram negative bacteria such as *E. coli*, contains a layer of outer lipopolysaccharides (1–3 µm thick) with peptidoglycan layer of approximate ~ 8 nm thickness inside. On the other hand, the gram positive bacteria, i.e., *S. aureus* have outer layer made of thick peptidoglycan (~ 80 nm), therefore the interaction of metallic nanoparticles with thick peptidoglycan can prove to be less detrimental than gram negative bacteria with thin peptidoglycan layer [8,5,25].

Moreover, as most of the nanoparticles release positive ions and the presence of outer lipopolysaccharides in gram negative bacteria carries negative charge, which can binds with positively charged ions released by metallic nanoparticles, causing disruption of cell wall and intracellular components. Silver nanoparticles generally affect the respiratory chain, cell division

and causing cell death. It was reported that the release of silver ions from silver nanoparticles are responsible for antibacterial activity. The silver ions inhibits the cellular and respiratory enzymes essential for ATP production, inducing ROS generation, leading to DNA damage and inhibition of ribosomal subunit proteins [1,22]. As it has more tendency to bind with sulfur or phosphorus, therefore proteins and DNA are the main targets. In the case of Copper nanoparticles, it was highlighted that due to lipid peroxidation and reactive oxygen species (ROS) generation, protein oxidation and DNA degradation in *E. coli* occurs [26,27]. As per ZnO nanoparticles damage bacterial cell membrane by affecting the permeability of membranes. The nanoparticles enters through membrane easily and induce oxidative stress, affecting cell growth, leading to cell death [28,29]. Similarly, Carre et al. [30] reported that the antibacterial photocatalytic activity of TiO₂ nanoparticles was resulted because of lipid peroxidation causing enhanced membrane fluidity, further resulting in damage to cell integrity in the case of *E. col*.

2.2 Antibiofilm Activity of Nanoparticles

Microorganisms can attach with the abiotic or biotic surfaces and secrete extracellular polysaccharide matrix. Further, the colony initiation starts inside the matrix, forming a mature biofilm. Within the biofilm, the bacteria remains protected and use mechanisms to evade the host immune response [32]. Moreover, bacteria becomes highly resistant to various applied antibiotics within the protection of biofilm. It was identified that the antibiotic concentration required to eradicate biofilm range from 100-1000 times from that of MIC needed to remove planktonic bacteria [33]. Various delivery strategies are used for the treatment of biofilm associated infections, i.e., antibiotic releasing hydrogels (increase specific site concentration, penetration and inhibition of biofilm) and Use of natural or synthetic peptides of antimicrobial properties. Recently research has shown that phage therapy can also control biofilm formation [11]. However, all the mentioned therapies/treatments have one or the other limitation, making them non-applicable. Therefore, it is important to identify and develop the reliable and efficient technology for the control of biofilm. Literature studies have highlighted the potential of nanoparticles in controlling the biofilm formation on various surfaces (Table 1), especially on medical devices and implants [34,35].

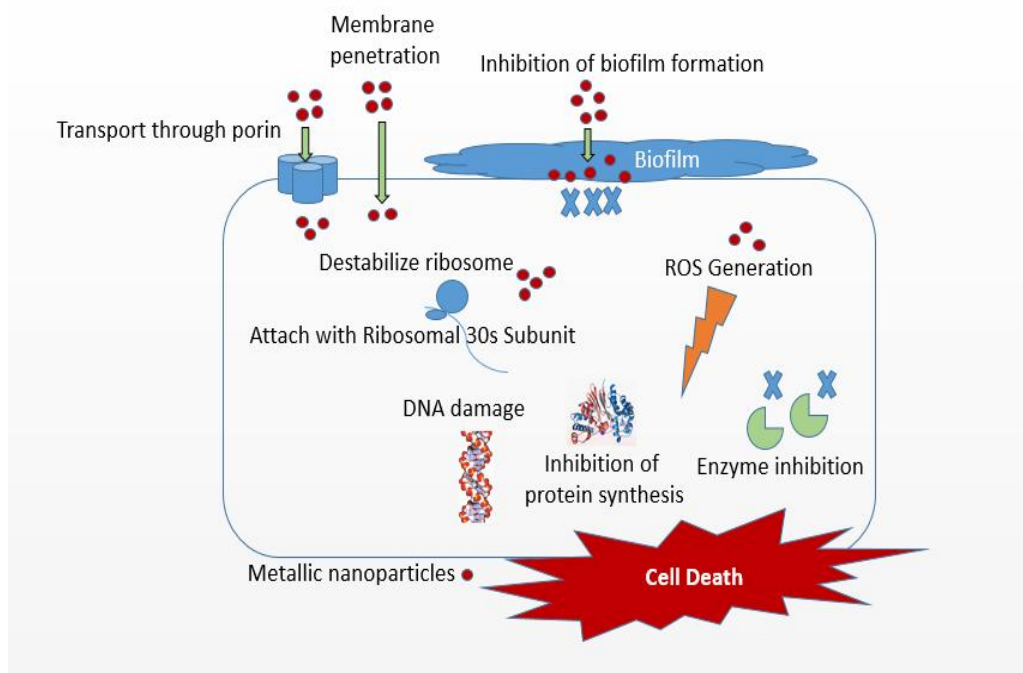


Fig. 1. Antibacterial mechanism of nanoparticle

{Modified from Baptista et al. [31]; Garg et al. [1]}

Estevez et al. [36] highlighted the disruption of *E. coli* and *C. albicans* biofilms and also the loss in cell membrane integrity with the treatment of silver nanoparticles synthesized from extracellular cell free extracts of *Phanerochaete chrysosporium*. In a study, Heinonen et al [37] observed 88 % reduction in bacterial adherence onto steel surface with superhydrophobic silver nanoparticle coating. In another study, 4, 6-diamino-2-pyrimidinethiol-modified gold nanoparticles (Au-DAPT) when coated with aligners, a decrease in the planktonic cells was observed with prevention in biofilm development [38]. Further, incorporation of copper oxide nanoparticles in the soft denture liners highlighted a significant decrease in the colonization and accumulation of *C. albicans* [39]. Moreover, TiO₂/ZnO nanostructure coating showed efficient antibacterial and cytocompatibility activity [40].

The exact mechanism of anti-biofilm activity of nanoparticles is still not fully understood, however studies proposed that small sized nanoparticles (~15 nm) can directly interact and easily penetrate the EPS and water channels [11]. In addition, studies have also showed that microbial synthesized nanoparticles, such as AgNPs, AuNPs, TiO₂, ZnO etc., inhibit quorum sensing cascade [12,13]. Ali et al. [41] revealed

that AgNPs can inhibit LasI/Rhl I synthase in *P. aeruginosa*, thereby blocking the synthesis of signalling molecules, leading to the inhibition of quorum sensing. Samanta et al. [13] also highlighted that AuNPs can inhibit the metabolic activities and production of EPS, thereby helps in the prevention of biofilm formation. In another study, Naik and Kowshik [42] reported the efficient antiquorum sensing of AgCl-TiO₂ NPs against *C. violaceum*. The nanoparticles generally possess the ability of down regulating the quorum sensing genes, ZnO NPs were found to affect the genes responsible for quorum sensing, i.e., lasR, lasI, rhl I and rhl R in *P. aeruginosa* [43]. As per the latest available data, the interference in quorum sensing of microorganism by nanoparticles plays significant role in suppressing the biofilm formation, involving the inhibition and disruption of quorum sensing signals, and also blockage of quorum sensing receptors [12].

3. NANOTECHNOLOGY VS. ANTIBIOTIC RESISTANCE

Antibiotic resistance has now becoming a serious threat for the world, it's a great challenge which needs immediate attention. However, researchers are finding ways to overcome the problem of antibiotic resistance. As per recent

findings, nanotechnology has shown great promise to overcome the challenge of antibiotic resistance (31, 33). It has shown that the small sizes and higher surface-to-volume ratio helps the nanoparticles to interact with microbes more effectively. Further, it has been suggested that the development of bacterial resistance against nanoparticles is difficult, as nanoparticles target multiple sites and various biomolecules in bacterial cells [25]. The high antibacterial properties of nanoparticles of silver, titanium oxide, copper oxide, zinc oxide, and iron makes them the preferred nanoparticles and further they are also found to be suitable delivery agent of drugs/antibiotics. Recent studies have suggested that metal nanoparticles, i.e., gold nanoparticles, can be used as an efficient drug-delivery system [44].

The control of antibiotic-resistant bacteria generally requires variety of costly drugs which may have side effects. Due to this, the treatments becomes expensive and need more time. Nanoparticles can offer the natural multi-targeted strategy to control the multidrug-resistant bacteria (Table 2). In a study, Percival et al. [45] have tested the antimicrobial activity of nano-silver containing dressing against antibiotic resistant bacteria. The study highlighted the efficient antibacterial activity of silver nanoparticles with inhibition of biofilm formation. Further, in drug resistant strains of *P. aeruginosa*, the chemically synthesized silver nanoparticles showed 56% inhibition in biofilm formation [55]. In comparison to silver nanoparticles, gold nanoparticles possess weak antimicrobial activity, however Li et al. [56] reported that tuning the functional group on the surface of gold nanoparticles can be used against Multi drug resistant (MDR) and methicillin-resistant (MR) *S. aureus*. In another study, Govindaraju et al. [57] highlighted the importance of glucosamine-functionalized gold nanoparticles (GlcN-AuNPs) for antibacterial activity. The study reported that laser-irradiated GlcN-AuNPs have efficient antibacterial activity for *E. coli*. The study showed potential to treat variety of bacterial diseases. In another study Zhu et al. [58] developed a method to prepare 4,6-diamino-2-pyrimidinethiol-functionalized gold nanoparticles, DAPT-Au NPs (composite film) and a silk fibroin (SF) mixed-matrix membrane (DAPT-Au-SF MMM) for wound dressing material to treat MDR strain of *E. coli*. The study showed that DAPT-Au-SF MMMs is effective in healing rat wounds infected with MDR *E. coli*.

Talib et al. [59] synthesized copper nanoparticles from fruit extracts of *Ficus* sp., the study observed efficient antimicrobial activity against MDR clinical isolates bacteria. Navale et al. [16] studied the antimicrobial effects induced by synthesized ZnO-NPs in *S. aureus*, *S. Typhimurium*, *Aspergillus flavus* and *A. fumigatus*. A 20-25 nm sized ZnO-NPs presented substantial antimicrobial effects on the studied fungi and bacterial strain, the study also confirmed the generation of ROS. On the other hand, Agarwala et al. [60] assessed the antimicrobial efficacy of Copper oxide and Iron oxide (III) nanoparticles against biofilm forming bacterial strains. The results highlighted superior activity of CuO nanoparticles than Fe₂O₃ nanoparticles with better efficacy observed for MRSA followed by *E. coli* with CuO nanoparticles. Titanium dioxide nanoparticles were also studied for antimicrobial activity and Beyth et al. [61] reported the efficient action of TiO₂ nanoparticles on both gram positive and negative bacteria. The susceptibility of extremely drug-resistant (XDR) *P. aeruginosa* was demonstrated by TiO₂ nanoparticles [14].

Studies proved that the use of drugs with smaller nanoparticles prevents the resistance development against variety of pathogens [62]. Gelperina et al. [63] highlighted that the nanoparticles can be developed to provide control drug release. Moreover, bioavailability of drug and decrease in the frequency of drug dose can be obtained, if drugs will be used in combination with nanoparticles. In a study, Mohamed et al. [64], reported a strong antibacterial and biofilm eradication efficacy of AgNPs alone and in combination with vancomycin (in low doses) against multidrug resistant and biofilm forming pathogens, i.e., *S. aureus*, *P. aeruginosa* and *S. pneumoniae*. The study suggested that the use of AgNPs in combination with antibiotic and its possibility as final line of treatment against MDR pathogens. A recent study highlighted that fungal infections can be treated well even with low drug dose, when nanoparticle and drug combination was used [65]. Reports also showed that organic nanoparticles can also be effective and found to reduce the side effects of various drugs (acyclovir, amphotericin B) [66,67]. Due to biofilm, many drugs cannot penetrate and reach to the site of infection, however in a study, Baelo et al. [68] found that the combination of nanoparticle + drug can penetrate the hard biofilm and provide effective treatment.

Table 1. Antibacterial/Antibiofilm activity of different nanoparticles

S.no	Type of nanoparticle	Source of synthesis/ Method	Size (nm)	Shape	Activity	Result	Reference
1.	Silver	<i>Moringa oleifera</i>	4	Spherical	Antibacterial	ZOI Assay <i>E. coli</i> - 30.6 mm <i>P. aeruginosa</i> – 22.8	[46]
2.	Silver	<i>Artemisia kapetdaghensis</i>	3- 35	Spherical	Antibacterial	ZOI Assay- <i>K. pneumonia</i> - 22.3 mm <i>S. aureus</i> -17.8 mm	[47]
3.	Silver	<i>Cedecea Sp.</i>	10- 40	Spherical	Antibiofilm	Stronger antibiofilm activity for <i>E. coli</i> and <i>P. aeruginosa</i> ; Weak activity for <i>S. aureus</i> and <i>S. epidermidis</i>	[48]
4.	Gold	Banana pith extract	200-500	–	Antibacterial	ZOI Assay- <i>E. coli</i> > <i>Bacillus sp.</i> > <i>Pseudomonas sp.</i>	[49]
5.	Gold	<i>Cinnamomum zeylanicum</i> leaf extract	–	Triangular And Spherical	Antibacterial	ZOI Assay- Triangular Nps showed higher activity than Spherical Nps against gram negative and gram positive bacteria	[50]
6.	Iron	<i>Eucalyptus robusta</i>	0.2- 2	Spherical	Antibacterial	ZOI Assay <i>B. subtilis</i> more sensitive than <i>E. coli</i> , <i>S. aureus</i> and <i>P. aeruginosa</i>	[51]
7.	Copper	One pot synthesis	55	Spherical	Antibiofilm	Concentration of 100 ng/ml prevent biofilm formation	[52]
8.	Copper	Citus lemon fruit	30	Spherical	Antibacterial	ZOI assay <i>E. coli</i> - 25 mm <i>S. aureus</i> - 20 mm	[3]
9.	Zinc oxide	<i>Eucalyptus globus</i> essential oil	40	Spherical	Antibacterial & Antibiofilm	Agar well diffusion method- <i>K. pneumonia</i> -19.35 mm. In antibiofilm assay- 85 % and 97 % reduction was observed in <i>S. aureus</i> and <i>P. aeruginosa</i> , respectively.	[53]
10.	Titanium dioxide	<i>Aloe barbadensis</i>	20	–	Antibacterial & Antibiofilm	Antibacterial-MIC- 31.25 µg/ml for <i>P. aeruginosa</i> . Antibiofilm- Inhibition of 30.69 % at a concentration of 31.25 µg/ml	[54]

Table 2. Nanoparticles for antimicrobial/antibiofilm activity against antibiotic resistant microorganisms

S.no	Microorganisms	Type of antibiotic resistance	Antimicrobial/ Antibiofilm agent	Reference
1.	<i>S. aureus</i>	MRSA	AgNPs synthesized from Streptomycin sp.	[69]
	<i>N. gonorrhoea</i>	Tetracycline		
2.	<i>S. aureus</i>	MDR	TiO ₂ NPs synthesized from <i>Ochradenus arabicus</i> leaf extract	[70]
	<i>P. aeruginosa</i>			
3.	<i>P. aeruginosa</i>	MDR	ZnO NPs synthesized from seed extract of <i>Butea monosperma</i>	[71]
4.	<i>S. aureus</i>	MRSA	Ag-ZnO NPs (Bimetallic) One pot synthesis	[72]
5.	<i>P. aeruginosa</i>	MDR	Ag/AgO ₂ hybrid NPs AgNPs synthesized from <i>Kitasatospora albolonga</i> strain	[73]
6.	<i>P. aeruginosa</i>	XDR	TiO ₂ NPs synthesized from <i>Tricoderma</i> sp.	[14]
7.	<i>Monilinia fructicola</i>	Benzimidazole	CuNPs	[74]
8.	<i>E. coli</i>	Ampicillin	AuNPs	[75]

4. NANOPARTICLES AND TOXICITY CONCERNS

Different types of nanoparticles bearing different shapes and size have been recognised for effectiveness in controlling infectious microbes. However, their use is still limited in current treatment procedures. The main concern with the use of nanoparticles is the associated toxicity to normal human cells. The detailed research to identify the proper application with identification of safe and effective dose is under process. Recently, Sruthi and Valappil [76] reported the distribution of ZnO NPs in kidney, heart, liver, lungs and spleen when given intravenously. As per study, inflammation in tissues and histopathological lesions were observed after ZnO NPs interaction. In a study, Li and Cummins [77] highlighted that AgNPs can persist in human body for long periods, and attention is required for neurotoxicity and reprotoxicity issues. For TiO₂ NPs, which are generally used in cosmetics and skin products, have been reported for low cytotoxicity on HaCaT keratinocytes. The study suggested that TiO₂ NPs can be toxic after long term exposure only [78]. A study on animal model reported that when mice exposed to AuNPs, formation of liver granulomas occur with increased pro-inflammatory cytokine interleukin-18 in serum [79]. Further, the induction of oxidative stress with damage on mitochondrial and lysosomal membrane was reported with exposure of CuO Nps [80]. Therefore, more detailed research on toxicity of different nanoparticles is required to understand the associated short and long term harmful effects before using them into regular healthcare practices.

5. CONCLUSIONS

With concerns over increasing antibiotic resistance among bacterial species, the alternative strategy to combat these challenges has begun from last decade. As per research, it has been identified that nanotechnology holds the promise to tackle various hurdles (adherence, biofilm formation and antibiotic resistance) presented by different pathogenic microbes. Different nanoparticles of various shape and size can offer different grades of protection, generally small sized nanoparticle (<30 nm) can be very effective in interacting with membrane and causing bacterial cell damage. Studies have highlighted that nanoparticles especially nano-silver is very effective coating material in surgical instruments, implants and

catheters. These nano-coatings are also observed to be stable and possess efficient antibiofilm/antibacterial properties. Recent advancement showed that nanomaterials can also be used as an efficient drug delivery carriers, referred to as nanovehicles, which can specifically target the drug molecule to its location, therefore found to be better and superior antimicrobial agent than conventional antimicrobial therapies. Further, more research is required to understand the antibacterial mechanisms of nanoparticles which could be helpful in designing more specific, effective and controlled strategy to fight better with microbial pathogens. Moreover, issues related to the toxicity of nanoparticles should be considered before integrating them with conventional medical therapies.

6. FUTURE PROSPECTS OF ANTI-MICROBIAL NANOTECHNOLOGY

The development of resistance for antimicrobial agents is recognized as one of the major threat for public health and safety by WHO. Therefore, designing more effective strategies, while discovering newer class of drugs, and identifying the methods for specific targets has already begun. In line with these developments, nanotechnology has been identified and now considered as the best solution for this challenge. In recent years, many new ideas, designs and strategies have been tested/under process for the feasibility and integration with current system of treatment. At present, in order to prevent the resistance development, the decrease in antibiotic dose, while increasing the bioavailability to the target site is considered to be a good approach. Metallic nanoparticles have already showed potential to conjugate with antibiotics and provide synergistic effects. Therefore, many metallic nanoparticles, especially nano-silver is already in use as a coating material for surgical instruments and implants.

Moreover, recent reports have suggested the development of functional polymer nanomaterials for enhancing the efficacy of antimicrobials. It is considered that these polymeric nanomaterials (vesicles, hydrogels, and micelles) can be used as encapsulated material for conventional antibiotics and targeted towards specific infection site, which will eventually produce slow and sustained release of drug. Further, research has also highlighted the development of nanomedicine based antimicrobial peptides

(AMP). These AMPs include, metallic, non-metallic, liposomal and polymeric nanoparticles along with their hybrids, research is under process to study the nature, stability and efficiency of these systems. Further, photodynamic therapy (PDT) which is used for various infections can be improved by nanotechnology, by integrating nanoparticles with PDT. The improved system provide better penetration and delivery to the target site. The battle against pathogenic microbes and their different mechanism require many strategies to work together in achieving the success over antimicrobial resistance.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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