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Review article

ROLE OF NANOPARTICLES IN ELIMINATION OF BIOFILM PRODUCED BY PATHOGENIC BACTERIA

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ABSTRACT

Biofilm is a structured conglomeration of bacteria entrenched in a polymer matrix that is self-produced and contains DNA, polysaccharide, protein, and cause chronic infections. *Pseudomonas aeruginosa* lung infection is one of the well stated examples of pathogenic biofilms in cystic fibrosis patients. Due to mutating nature of the pathogens high antibiotic resistance will develop that make antibiotic treatment ineffective against repeated infections that are related to indwelling medical devices. Normally it was considered that nanoparticles are not larger than 100 nm, and their development to fight infection has gained popularity over the several decades. Different types of nanoparticles were introduced to treat biofilm infections in which silver nanoparticles were considered to be more efficient than all others. Maximum zone of inhibition in case of silver nanoparticles was found to be 40 mm against *S. aureus,* whereas maximum zone of inhibition with ZnO nanoparticles was 16 mm against *Campylobacter jejuni,* while in case of selenium nanoparticles and iron oxide nanoparticles zone of inhibition was time dependent and concentration dependent respectively. The order of antibacterial activity was like that Ag-Np>ZnO>CuO>Fe_2O_3. In this review article we discussed different biofilm producing pathogens that were isolated from different locations in latest research and to evaluate the role of nanoparticles in eradicating these pathogenic microbes.

Keywords: Biofilms, Nanoparticles, Silver nanoparticles, Zinc oxide nanoparticles, *Staphyloccocus aureus*

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INTRODUCTION

Bacteria exhibit two apparent forms of life. In one form, they are present as single, free cells while in other form they are organized into collective sessile. The second form is usually termed as biofilm mode of growth **[1].** Biofilms are meticulous accumulations of microorganisms connected with surfaces that have been extensively studied from the last few years partly because 65% or more of all infections are chiefly caused by these biofilms such as device-related infections, infections on body surfaces and chronic infections **[2].** *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, Streptococcus viridians* and *Klebsiella pneumoniae* are the most prominent biofilm-forming bacteria **[3]** in which *Pseudomonas aeruginosa* caused infections in the patients with cystic fibrosis (CF) **[4]**, *Staphylococcus epidermidis* and *Staphyloccocus aureus* caused medical implant-related infections and plaque formation on teeth **[5].** Currently such device-related infections (DRIs) are widespread source of healthcare-associated infection (HCAI). Previous data showed that DRIs were caused due to biofilm development and was well accepted. Device related infections arise when microorganisms rip off **[6].** Chronic infections are caused by biofilm growing bacteria **[1]** which are identified by endure inflammation and tissue damage, Chronic infections, together with foreign body infections **[2].** The National Institutes of Health states that there are approximately 80% of all infections related to biofilm. And these infections are related to chronic inflammation and are resistant to the immune system **[7]**. Attacking antigens can easily become hidden in the biofilm, concealing the sites on which antibiotic is going to target. Moreover, genetic material can be switched between members of different biofilms, which increases

variety, permitting adoption to new pathological niche and providing with better survival **[8].** Despite conventional antibiotics that have lot of disadvantages like i) development of resistance ii) less therapeutic index iii) cytotoxicity iv) problem associated with route of administration, etc. These problems can be resolved by using alternate delivery systems like nano-technology **[9].** The future of nanoparticles to control the formation of biofilms, is now under keen interest. Specially, the use of nanoparticulate zinc, silver, copper would be studied for their effects on bacterial populations **[10].** Here, we explain the role of different types of nanoparticles to encounter the problem of antibiotic resistance.

OCCURRENCE AND ARCHITECTURE OF BACTERIAL BIOFILMS

Foreign body infections are identified by the presence of biofilm the liable bacteria or fungi on the external or internal surfaces of foreign body. Biofilm developed on natural surfaces like teeth **[11]** heart valves **[12]** in lungs of cystic fibrosis patients **[13]** in chronic rhinosinusitis, in the middle ear in patients with chronic and secretory otitis media **[14]** in chronic wounds **[15]**, in intravenous catheters and stents **[16]**. This kind of microbes in biofilms are typically kept together by a self-produced biopolymeric matrix. The matrix is self-produced extracellular material in which the cells of biofilm are fixed. It reside as agglomeration of different kinds of biopolymers known as extracellular polymeric substances (EPS) that provide platform for three-dimensional architecture of biofilm and is responsible for attachment to surfaces and pulling together in the biofilm. Biofilm cells are immobilized by EPS and it kept them in close proximity, thus allow for deep interactions, together with cell to cell contact, and the creation of harmonious microconsortia. EPS thus called 'the dark matter of biofilms' due to big range of matrix biopolymers it is more complicated to analyze them **[17].** Naturally biofilms are present on many organs and act as normal flora. When connection with any foreign body occur then it produced pathogenic effects (diseases). According to different researches it was observed that there are 2 types of infections caused by biofilm such as tissue related infections and device related infections (**Table 1).**

BIOFILM DEVELOPMENT

The study of biofilm formation showed that it take place in three principal stages (1) binding to surfaces (2) propagation and development of typical mature biofilm framework (3) dissolution often termed as scattering **[24]**. Commonly, attachment take place easily on surfaces that are bumpy, and painted by surface conditioning films**.** Properties of the cell surface, especially the presence of extracellular appendages, the connections occur in cell-cell communication and expansion. The primary, reversible communication among a bacterial cell and a surface is interceded by general Lewis acid-base, electrostatic and Lifshitz-van der Waals forces. This temporary interaction is assisted by host and tissue specific bond that are situated on the bacterial cell surface or on cellular projections like pilli and fimbriae. After connecting to tissues or matrix-covered devices is adept, this toxic bacterial biofilm become larger by propagation and creation of extracellular matrix. Adhesion is supplied by matrix between bacterial cells, as a result of this adhesion a multilayered biofilm is formed **[25].**

Table 1: Natural and pathogenic biofilms on tissue and foreign bodies.

Natural biofilms	Connection via foreign bodies	Pathological biofilms	Pathology (outcomes)	Ref
Skin	Tissue related infections	Middle ear	CSOM (Chronic suppurative otitis media chronic sinusitis)	**[14]**
		Blood	Chronic wounds, Bacteremia	**[15]**
		Peritoneum	Peritonitis	**[18]**
Mouth		Teeth	Dental plaque	**[11]**
Pharynx		Bronchi	Chronic laryngitis	**[19]**
		Lungs	Cystic fibrosis	**[13]**
Duodenum		Bile tract	Gall bladder infections	**[20]**
Urethra		Urinary bladder	Urethritis, cystitis	**[21]**
Vagina		Uterus	Urinary tract infections, vaginosis	**[22]**
Air in operation room	Device related infections	Prosthetics pacemakers and grafts	Ventricular diseases	**[12] [23]**
		Catheters		**[23]**
		Urinary catheters and prosthetic joints		**[23]**

Table 2: The pathogenic effects produced by biofilm producing bacteria.

Bacteria	Isolation	Pathogenic effect	Location	Ref
Pseudomonas aeruginosa	Lung tissues	Cystic fibrosis	Lungs	**[31]**
	From patients of Post-operative endophthalmitis	post-operative endophthalmitis	Eyes	**[31]**
E. coli			Catheter related UTI	**[32]**
Streptococcus mutans, Streptococcus sobrinus and Lactobacillus	Mesial aspect of teeth	Dental caries and	Oral cavity plaque formation	**[33]**
Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola	Mesial aspect teeth	Advancing periodontitis	Oral cavity	**[33]**
Salmonella typhi	Gall bladder tissues and stool samples	Typhoid, Cholicystitis	Intestines, Gallbladder	**[20]**
M. tuberculosis	Sputum samples	Human tuberculosis	Lungs	**[34]**
Staphylococcus aureus	Patient skin microflora	Nosocomial infections skin and soft tissue infections, endocarditis or osteomyelitis	Skin and soft tissues	**[26]**
Staphylococcus epidermidis	Indwelling devices	Catheter related infections	Foreign device i.e catheter	**[35]**

The primary components of biofilm formation in *S. epidermidis and S. aureus* was polymer of N-acetyl glucosamine (PNAG) also mentioned as polysaccharide intercellular adhesin (PIA), to design biofilms **[26].** In *B. subtilis* TasA a single major protein that was associated with extracellular matrix. It is currently revealed that TasA form extracellular fibers that have amyloid–like characteristics and is reflected to play fundamental or structural role in the extracellular matrix. The matrix of *P. aeruginosa* biofilm consists of three exopolysaccharide – alginate, Psl and Pel **[27]**. Besides providing an anatomical 'platform' for the biofilm colony, the matrix also promote biofilm mediated antimicrobial resistance, either by obstructing the dispersion or directly bind to antimicrobial agents and prevent their contact to biofilm cells**.** Prolonged growth of bacteria on surface causes the formation of mature biofilm consisting of millions of firmly packed cells into pier and sprout shaped masses extending outward **[28].**

In the last stage there is separation of cells and they get scattered into environment **[29].**

PATHOGENIC EFFECTS OF BIOFILMS

Chronic *Pseudomonas aeruginosa* infections in lungs with cystic fibrosis occur again and again due to formation of mucoid strains by biofilm **[13].** Chronic, nonhealing dermal wounds were global dilemma, and were associated with significant patient morbidity**.** All wounds other than new surgical wounds are settled by microorganisms and it is acknowledged that microorganisms reside in the tissue of all chronic wounds **[30].**

In the above table different biofilm producing microbes that were isolated from different body tissues by different researchers and a specific microbe caused a specific disease. In case of cystic fibrosis. Høibya found that the causative agent of this disease was *pseudomonas aeruginosa* **[36]**. Another researcher LaPlante searched out that catheter related to UTI were caused by *E. coli* **[37]** but in case of dental carries, plaque formation and advancing periodontitis there were different causative agents found on mesial aspect of teeth by Allaker **[33]**. Research work of Chakraborty showed that *M. tuberculosis* was present in sputum samples of tuberculosis patients **[33]**. Fey found that subcutaneous, skin infections and soft tissue inflammations were caused by *S. aureus* and in case of catheter related infections the major causative agent was *S. epidermidis* **[26]**.

MUTATORS

Bacterial biofilms show more resistance to antimicrobial agents than planktonic cells. This characteristic makes it hard to eradicate infections, represent a severe medical problem**.** In the mature stage biofilm structures showed highest resistance to antibiotics **[36].** A number of mechanisms are

apparently accountable for the antimicrobial resistance in biofilm structures:

(1) Reduced diffusion of antibiotics throughout polysaccharide matrix of biofilm; (2) Physiological changes occurred because of less development in growth rate, nutrient deficiency or ecological pressure;;(3) The cells that forming the biofilms phenotypically changed; (4) Quorum-sensing, though their precise role is not clearly known; (5) Expression of efflux pumps are changed; (6) Persister cells: minute fractions of persistent bacteria showing resistance when exposed to antimicrobials **[38]**.

Different biofilm producing bacteria showed resistance against different antibiotics. Different antibiotic resistance pattern was observed for e.g against *S. aureus, E.coli P. aeruginosa* and *S. pneumoniae* etc and this antibiotic resistance was produced by multiple factors. Researchers found that *S. aureus* showed resistance against many antibiotics such as Gentamicin, clindamycin, erythromycin, co-trimoxazole, nitrofurantoin, quinolones, tetracyclins, glycopeptides and vancomycin **[39, 41]**. Similarly some observed that *E.coli* showed resistance against many antibiotics as fluoroquinolones, rifampicin, tetracycline, sulfonamide, ampicillin, streptomycin, cephalothrin, chloramphenicol, nitrofurantoin **[40, 42]**. Other biofilm producing bacteria *S.pneumoniae* have resistance to some antibiotics like erythromycin and penicillin. The most important pathogenic biofilm producing bacteria *P. aeruginosa* showed highest resistance to many antibiotics such as gentamicin, tobramycin, ciprofloxacin, B. lactam antibiotics (Ceftazidime Imipenem, meropenem) penicillins, cephalosporins, (carbapenems, ureidopenicillins) quinolone, tobramycin and colistitin **[41].**

EFFECT OF NANOPARTICLES

Rise of infectious disease is a deadpan warning to public health globally, particularly with the development of antibiotic resistance in bacterial strains. Medical device related infections appear repeatedly and have high cost depends on the device handling and period of use. Such infections are shown for joint prostheses, venous catheters and, endotracheal tubes (ETT), Prosthetic heart valves etc **[45].** Inside mouth microbial communities exist mostly as biofilms. These biofilms are usually found attached over the teeth, on some type of prostheses, and surface of mucosal layers. In this location these biofilms are very much prone to cause number of diseases like dental caries, periodontal infections, candidiasis and implant infections etc **[46].** Nanoparticles have been broadly studied for a wide range of therapeutic purposes. Nanoparticles due to their high surface-to-volume ratios and nanoscale sizes are more advantageous **[47].** Reduction in size of these particles such as from a micrometer to nanometer, the resulting properties can change significantly**.** In general, the cell cytotoxicity mechanisms for metal nanoparticles are verified to be reactive oxygen species (ROS) production **[48].**

Silver Nanoparticles

Silver nanoparticles were successfully employed as antimicrobial agents. Four pathogenic test strains in which maximum zone of inhibition against *E. coli* was 32mm, in *P. aeruginosa* was 29 mm, in *Staphylococcus aureus* CCM 3953 was 34 mm and in *Staphylococcus aureus MRSA* was 40 mm **[48]**. Researcher used two types of biogenic silver nanoparticles synthesized with gum ghatti and gum olibanum and they found that the maximum zone of inhibitions with Ag-gum ghatti were 12.2 mm against *S. aureus,*11mm against *P. aeruginosa* and 9.0 mm against *E. coli*, while in case of Ag- gum olibanum observed zone of inhibitions were 10.7 mm,7.5 mm,8.0 mm against *S. aureus, P. aeruginosa* and *E.coli* respectively. It was suggested that from the above results the maximum zone of inhibition in case of silver nanoparticles was 40 mm against *S. aureus* while minimum zone of inhibition was 5mm against *P. aeruginosa.* So silver nanoparticles are more effective against *S. aureus* than other biofilm producing bacteria **[51]**. The MIC was 12.5 ug/mL for gram positive bacteria and 50 ug/mL against gram negative bacteria **[49]**. It was showed that MIC and MBC required to inhibit the growth of *S. pyogenes* was same 66.7mM and 83.3 mM MIC and MBC was required to inhibit the growth of *E. coli.* In case of *P. aeruginosa* MIC was 83.2mM while MBC required to kill the bacterial growth was 100.0 Mm. It is suggested that more quantity of silver nanoparticles would be required to kill the biofilm producing bacteria against *P. aeruginosa* than all others **[50].**

Zinc Oxide Nanoparticles

The antibacterial activity of ZnO has been calculated basically with diverse pathogenic and nonpathogenic bacteria such as *S. aureus* and *E. coli.* The minimum inhibitory concentration generally was 2-7 mM against following bacterias *Staphylococcus epidermidis; Streptococcus pyogenes N315; Enterococcus faecalis; Bacillus subtilis; and B. cereus) and* Gram-negative *(Escherichia coli, Proteus vulgaris Salmonella typhimurium, Shigella flexinari, Pseudomonas alcaligenes, and Enterobacter aerogenes)* **[52]**. The MIC of ZnO was $\geq$0.03 mg/ mL to inhibit the *Campylobacter jejuni* **[53]**. While maximum zone of inhibition was 12 mm against *S. aureus* and growth reduction occurs in *E. coli* **[55]**.

Table 3: Different biofilm producing bacteria that are resistant to different antibiotics and their mechanism of action.

Bacteria	Antibiotic	Mechanism of action	Ref
S. aureus	Nitrofurantoin, Gentamicin, Clindamycin, Co-trimoxazole Erythromycin	-	**[40]**
S. aureus	Tetracyclins Quinolones	NorA, NorB and NorC are MDR pumps 2) ant Tet	**[40]**
S. aureus	Glycopeptides Vancomycin	Inhibition of peptidoglycan Synthesis	**[41]**
E. coli	Ampicillin, Sulfonamide, Tetracycline, Streptomycin Cephalothrin, Chloramphenicol Nitrofurantoin	-	**[39]**
E. coli	Ciprofloxacin Fluoroquinolones	PMQR *qnrA, qnrB, qnrS1* Mutation in QRDRs *gyrA*	**[42]**
E. coli	Chloramphenicol, Fluoroquinolones, Rifampicin, tetracycline	AcrAB-TolC system putative multidrug resistant pump YhaQ	**[40]**
S. pneumoniae	Macrolides Erythromycin	Inhibition of protein synthesis by interrupting binding to ribosomal subunits.	**[41]**
	B-Lactams Penicillin	Interruption of cell wall synthesis	**[41]**
P. aeruginosa	B-Lactam antibiotics Meropene Imipenem Ceftazidime	1) Function of HSI-I T6S system tssC1 gene 2) Involvement of OprD, AmpC, and efflux pumps	**[43]**
P. aeruginosa	Penicillins penicillins, Cephalosporins Cephalosporins Penicillins	B-Lactamase AmpC ESBLs, Metallo-b-lactamases	**[43]**
	Cephalosporins, Cephalosporins, Carbapenems, Aminoglycosides, Quinolones	Efflux pumps	
	Carbapenems, Aminoglycosides, Quinolones	Outer membrane impermeability	**[44]**

Legends: PMQR- Plasmid-mediated quinolone resistance, QRDR- Quinolone Resistance Determining sources Regions, MDR- Multidrug resistance

Table 4: The mechanism of action and antimicrobial effect of different nanoparticles.

Nanoparticles	Antimicrobial effects/potential	Target organism	Mechanism of action	Ref
Silver nanoparticles	12 ± 1.2 mm (zone of inhibition) 9.5 ± 0.9 mm (zone of inhibition)	*S. epidermidis* *P. aeruginosa*	AgNPs directly diffuse from the pores and prevent biofilm formation.	**49**
Silver nanoparticles	Zone of inhibition (mm) SHC-1 9 ± 1.0 SHC-2 10 ± 0.5 SHCS-1 26±0.5 SHS-1 32±0.7 SHC-1 9 ± 0.5 SHC-2 11 ± 0.3 SHS-1 29 ± 1.0 SHCS-1 19 ± 0.6 SHC-1 12 ± 0.4 SHC-2 11 ± 0.6 SHS-1 34 ± 0.5 SHCS-1 31 ± 1.0 SHC-1 11 ± 0.6 SHC-2 11 ± 1.0 SHS-1 40 ± 0.3 SHCS-1 29 ± 0.5	*E. coli* *Pseudomonas aeruginosa* CCM 3955 S*taphylococcus aureus* CCM 3953 *Staphylococcus aureus* MRSA	1) Interfering cell wall synthesis 2) Protein synthesis was inhibited 3) Halting nucleic acid synthesis 4) Disruption of a metabolic pathway	**49**
Bio-synthesized Bio/Ag NPs	MIC was tested on Gram-positive and Gram-negative bacteria of biogenic silver and ionic silver ranging from 12.5 to 50 mg/L	*Actinomyces oris* *Porphyromonas gingivalis* *Fusobacterium nucleatum* *Actinobacillus* *Actinomycetum*	Radical formation	**50**
Silver nanoparticles	The MIC and MBC of *S. pyogenes* MIC (mM) 66.7 (±16.7*)* MBC 66.7 (±16.7) *E. coli* O157:H7 MIC (mM)83.3 (±16.7) MBC (Mm) 83.3 (±16.7) MBC (Mm) 100.0(±0.0)	*Pseudomonas aeruginosa* *E. coli* and *Streptococcus pyogenes*	Inhibition of cell wall synthesis,	**51**
Silver ring-coated superparamagnetic iron oxide nanoparticles (SPIONs)		*Staphylococcus epidermidis*	Oxidative stress created by free radicals	
Silver nanoparticles	Inhibition zone of around 5 mm	*Pseudomonas aeruginosa*	reactive oxygen species (ROS)	**51**
Biogenic silver Nanoparticles	Zone of inhibition (mm)in case of Ag NP-GT *S. aureus* 12.2±0.2 *P. aeruginosa* 11.0 *E. coli* 9.0 In case of Ag NP-OB *S. aureus 10*.7±0.2 *P. aeruginosa 7*.5 *E. coli* 8.0±1.0	*Pseudomonas aeruginosa* *E. coli* and *S. aureus*	Intracellular ROS leakage of proteins Outer membrane damage	**52**
Zinc Oxide Nanoparticles	MIC was generally observed to be in the range of 4 to 7 mm	*Bacillus subtilis;* *Escherichia coli,* *Shigella flexinari,* *Pseudomonas alcaligenes,* *Proteus vulgaris,* *Salmonella typhimurium,* and *Enterobacter aerogenes)*	Production of ROS Disruption and disorganization of membranes	**53**

Zinc Oxide Nanoparticles	The MIC of ZnO nanoparticles for *C. jejuni* was 0.05 to 0.025 mg/ml Bacterial growth inhibit at ≥0.03 mg/ml of ZnO nanoparticle	*Campylobacter jejuni*	Disruption of cell membranes Oxidative stress	**54**
Zinc Oxide Nanoparticles	Zone inhibition with NPs *Pseudomonas* against *P. aeruginosa* (16mm)	*P. aeruginosa* *aeruginosa*	Reactive oxygen species	**55**
Zinc Oxide Nanoparticles	5 and 10mM of ZnO had 10 and 12mm inhibition zone against *S. aureus*, respectively, but caused growth reduction in *E. coli*	*S. aureus* *E. coli*		**56**
Selenium Nanoparticles	Growth of *S. aureus* inhibited in the presence of selenium nanoparticles after 3, 4, and 5 hours at 7.8, 15.5, and 31 g/ml respectively.	*Staphylococcus* *aureus*		**57**
Iron oxide nanoparticles	*S. aureus* growth inhibited at the highest concentration (3 mg/mL) of iron oxide nanoparticles at all time points	*Staphylococcus* *aureus*	Reactive oxygen species (ROS) production	**58**
Superparamagnetic iron Oxide Nanoparticles (SPION)	-	Antibiotic-resistant biofilms *Staphylococcus epidermidis* and *S. aureus*		**58**
Meta oxide nanoparticles	Order of antibacterial activity ZnO, CuO, and Fe_2O_3) ZnO >CuO > Fe_2O_3. bacterial growth inhibition against *B. subtilis*, ZnO=(25mm) CuO and Fe_2O_3 s 21 and 15 mm, *E. coli* zone of inhibition19, 15, and 3 mm for ZnO, CuO, and Fe_2O_3, respectively *P. aeruginosa* and *S. aureus*, where the maximum zone of inhibition was exhibited by ZnO followed by CuO and Fe_2O_3.	Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*)and Gram-positive (*Staphylococcus aureus*) and *Bacillus subtilis*		**59**

Legends: MBC- Minimum bactericidal concentration, MIC- Minimum inhibitory concentration, *MRSA*- methicillin resistant *Staphylococcus aureus*, G- gum ghatti OB-gum olibanum.

Selenium Nanoparticles

It is considered that selenium has different medical applications such as anticancer applications. Selenium as a dietary supplement has been proved to reduce the risks of several types of cancers such as prostate cancer, lung cancer, and esophageal and gastric-cardiac cancers. The growth inhibition was time dependent as time increases growth inhibition rate increase. They observed that growth of *S. aureus* were inhibited in the presence of selenium nanoparticles after 3, 4, and 5 hours at 7.8, 15.5, and 31 ug/mL respectively. Similarly Wang *et al*. observed that in coated paper towels 90% growth of *S. aureus* was inhibited in the presence of selenium NPs after 72 hours. So it is supposed that bacterial growth inhibition with selenium NPs was directly proportional to time.

Iron Oxide Nanoparticles

These nanoparticles also have found their vast application in the field of medicine and research because of its biocompatibility and magnetic properties. The growth inhibition of iron oxide NPs was concentration dependent. Highest concentration was 3mg/mL of iron oxide NPs on which maximum growth inhibition occurred of *S. aureus* **[60]**. It was observed that 0.15mg/mL of iron oxide NPs showed zone of inhibition against *E. coli, P. aeruginosa* and *S. aureus* were 26, 28, 29mm respectively. The maximum zone of inhibition was 29 mm and it was also concentration dependent. So as the concentration of iron oxide NPs increased the zone of inhibition increased **[57]**.

Metal Oxide Nanoparticles (ZnO, CuO, and Fe_2O_3)

It was observed that different metal oxide nanoparticles showed different antibacterial activity against different bacteria for e.g zone of inhibition against *B. subtilis* was 25,21,15 mm when treated with ZnO, CuO and Fe_2O_3 respectively. In case of *E. coli* observed zone of inhibition was 19,15,3 mm when treated with ZnO, CuO and Fe_2O_3 respectively. Similarly in *P. aeruginosa* and *S.*

aureus order of antibacterial activity was ZnO>CuO> Fe_2O_3. So ZnO showed more efficacy than CuO and Fe_2O_3 **[58].**

CONCLUSION

In this review article different pathogens that are specific for producing biofilm, studied from different recent articles. The role of nanoparticles to fight these pathogenic microbes has been reviewed. These nanoparticles with potential therapeutic effects on pathogenic microbes can be utilized in synthesizing medicines. It can serve as a key for treating diseases and infections associated with these pathogens. The future of nanoparticles to control the formation of biofilms, is now under keen interest. Specially, the zinc, silver, copper nanoparticles are of great importance because of their therapeutic efficacy. These can also help in encountering the antibiotic resistance.

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