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REVIEW

Nanomaterials for alternative antibacterial therapy

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Abstract: Despite an array of cogent antibiotics, bacterial infections, notably those produced by nosocomial pathogens, still remain a leading factor of morbidity and mortality around the globe. They target the severely ill, hospitalized and immunocompromised patients with incapacitated immune system, who are prone to infections. The choice of antimicrobial therapy is largely empirical and not devoid of toxicity, hypersensitivity, teratogenicity and/or mutagenicity. The emergence of multidrug-resistant bacteria further intensifies the clinical predicament as it directly impacts public health due to diminished potency of current antibiotics. In addition, there is an escalating concern with respect to biofilm-associated infections that are refractory to the presently available antimicrobial armory, leaving almost no therapeutic option. Hence, there is a dire need to develop alternate antibacterial agents. The past decade has witnessed a substantial upsurge in the global use of nanomedicines as innovative tools for combating the high rates of antimicrobial resistance. Antibacterial activity of metal and metal oxide nanoparticles (NPs) has been extensively reported. The microbes are eliminated either by microbicidal effects of the NPs, such as release of free metal ions culminating in cell membrane damage, DNA interactions or free radical generation, or by microbiostatic effects coupled with killing potentiated by the host's immune system. This review encompasses the magnitude of multidrug resistance in nosocomial infections, bacterial evasion of the host immune system, mechanisms used by bacteria to develop drug resistance and the use of nanomaterials based on metals to overcome these challenges. The diverse annihilative effects of conventional and biogenic metal NPs for antibacterial activity are also discussed. The use of polymer-based nanomaterials and nanocomposites, alone or functionalized with ligands, antibodies or antibiotics, as alternative antimicrobial agents for treating severe bacterial infections is also discussed. Combinatorial therapy with metallic NPs, as adjunct to the existing antibiotics, may aid to restrain the mounting menace of bacterial resistance and nosocomial threat.

Keywords: antibacterial, metallic nanoparticles, microbicidal, nanomedicines, microbial biofilms, antibiotic resistance

Introduction

Hospital-acquired bacterial infections, mainly caused by the nosocomial pathogens such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and so on, pose the foremost challenge to the well-being of a patient.[1] The bacteria counteracts the host's innate immune defense machinery,[2,3] which becomes the prime cause of death in patients confined to the intensive care unit (ICU), with weakened immune system, culminating in invasive bloodstream infections. The widespread use of broad-spectrum antibiotics[4] has led to the appearance of multidrug-resistant (MDR) isolates that further intricate the clinical problem as the bacteria spread epidemically among the patients. With the

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compromising efficacy of the available chemotherapeutics due to mounting drug resistance and the biofilm recalcitrance towards antibiotics, there is a pressing need to identify alternate drugs. In this respect, nanomaterials have shown promise owing to their unique physical and chemical attributes.[5–7] Their large surface area relative to volume enables intimate interactions with microbial membranes, as well as surface functionalization, which help in developing more effective antibacterial agents. Over the last decade, there has been a remarkable global focus on conventional as well as biogenic metallic nanoparticles (NPs) as innovative tools for combating the high rates of antimicrobial resistance. Chemotherapeutic drugs when given in combination with metallic NPs may result in a cumulative effect due to the antibiotic as well as the metal ions released from NPs. Moreover, the antibacterial agent may be used at a much lower dose than when administered alone, hence overcoming the problem of resistance and diminishing other undesirable side effects to some extent.[6,8] There has also been a paradigm shift in management of biofilms and MDR bacteria with polymeric nanocomposites and antibiotic-loaded polymeric NPs. Improved therapeutic efficacy with concomitant decline in side effects of antimicrobial drugs has also been achieved by surface modification of metallic NPs with ligands or antibodies for targeted delivery.

This review summarizes the immune evasion strategies and antibiotic resistance mechanisms employed by bacteria to survive in the host and the probable metallic nanomaterials-based bactericidal effects to fight against nosocomial pathogens. The antibacterial activities of biologically synthesized metallic NPs as well as polymeric nanocomposites and surface-modified NPs are also highlighted. The metal-based nanomaterials alone or functionalized with antibiotics when translated to clinics may show promise as next-generation nanotherapeutics against bacterial menace.

Gravity of the problem

Bacterial infections have emerged as the leading cause of the formidable rates of deaths in hospitalized and immunosuppressed patients, especially those in ICUs and those undergoing invasive operations, worldwide[1,4,9–11] as well as in parts of Saudi Arabia where the prevalence has been reported to be 31.7%.[12] The hospital-acquired infections manifest in a wide gamut of severe clinical ramifications, such as bacteremia, septic shock, ventilator-related pneumonia and massive soft tissue necrosis, and rapidly progress to systemic infections that eventually culminate in multiorgan failure and death.[13] The control measures including implementation of hygiene, patient isolation and environmental decontamination have proved ineffective in keeping the infection at bay. Improper use of antibiotics has favored an upward trend in the development of resistance to almost all the available drugs, further compounding the clinical problem.[9,14] The challenge to control these infections is augmented in MDR bacteria such as those producing extended-spectrum β-lactamases and carbapenemases (*K. pneumoniae* carbapenase) and in methicillin-resistant *S. aureus* (MRSA). Drug combination regimens have also proved ineffective due to formation of biofilms, agglomerates of bacterial colonies that adhere to a surface and resist traditional means of killing by avoiding contact with the antibiotics.[15] The bacteria survive in the biofilms for extended periods of time and are likely to be transmitted within the health care settings. The quandary of mechanisms of antibiotic resistance has retrogressed the clinical outcome and inflated the economic burden of infectious diseases, leaving the medical practitioners with few therapeutic options to address the emerging threat.[14] Furthermore, an arsenal of strategies has been employed by bacteria to subvert the host immune system, adversely impacting the surrogate markers of clinical course such as the length of hospitalization and hospital-related deaths.

Bacteria's stratagem: targeting the innate immune defense

The bacteria have evolved a diverse array of resistance mechanisms to disable key players of the host innate immune defenses for their survival (Figure 1A). They utilize a multitude of virulence factors that conjointly render substantial impediment to phagocytes (macrophages and neutrophils) recruitment and activation.[3] The bacteria parasitize host cells by arresting or reprogramming phagosomal maturation, by escaping maturing phagosomes or by withstanding the microbicidal properties of the phagolysosome. They acquire resistant proteins to withstand low pH environment of phagosomes. The bacteria escape neutrophils extracellular traps (NETs) and elude opsonophagocytosis, and the cytocidal effects of host's antimicrobial peptides (AMPs) and reactive oxygen species (ROS). They secrete proteases that cleave NETs, degrade AMPs and express detoxifying enzymes like catalase to neutralize ROS and convert them into less harmful compounds.[16] Bacteria may also impair ROS production. Bacteria trigger phagocytic death through pore-forming cytolysins and escape host complement deposition and activation.[2] They release complement-degrading and complement-inactivating enzymes and inhibit membrane attack complex polymerization, thereby impeding bacteriolysis. Self-colonization of bacteria to form biofilms further leads to immune subterfuge.[6] Bacteria subvert

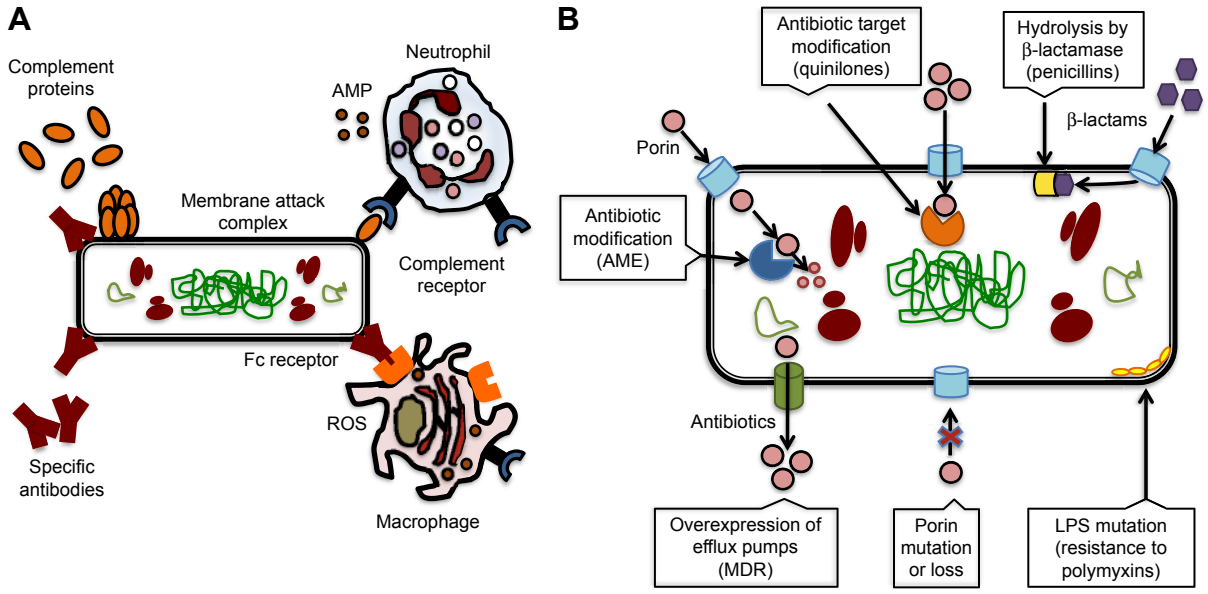

Figure 1 Strategies for survival in the host to spark invasive infections. (**A**) Innate immune mechanisms evaded by bacteria include phagocyte (macrophages, neutrophils) recruitment and activation, opsonization via Fc receptors on macrophages, complement activation and the bactericidal activities of antimicrobial peptides and reactive oxygen species. (**B**) Drug resistance mechanisms evolved by bacteria comprise hydrolysis by β-lactamases, modification of drug targets or antibiotics, loss or mutation of porins and overexpression of efflux pumps.
Abbreviations: AMP, antimicrobial peptide; ROS, reactive oxygen species; AME, aminoglycoside-modifying enzyme; MDR, multidrug resistant; LPS, lipopolysaccharide.

the T cell stimulation by dendritic cells (DCs), through downregulation of their antigen-presenting or costimulatory functions. Bacteria may directly infect DC, dampening its interleukin (IL)-12 and tumor necrosis factor-alpha (TNF-α) production, thereby crippling the adaptive immune response.[17] Immune evasion favors bacterial persistence, resulting in increased antibiotic use and selection for MDR pathogens, thus emphasizing the need for alternate antimicrobial therapies.[16]

The emergence of antibiotic resistance

In the present era, the quintessential antibiotics remain the mainstay for management of invasive infections, to annihilate or restrain the growth of a vast spectrum of bacteria. However, this perspective advocates ever-expanding threats accountable to indiscriminate use of antimicrobials resulting in escalated incidence of antibiotic resistance and epidemics of hypervirulent pathogens among vulnerable patients.[14] Bacteria have progressively eroded the effectiveness of not only a single antibiotic by developing resistance but concurrently multiple drugs that were previously effective. Intracellular bacteria are difficult to treat with regular antimicrobial therapies, resulting in chronic infections. Medical devices such as catheters, implants and sutures increase the risks of nosocomial infections due to formation of biofilms. The biofilm-related infections are extremely defiant to antimicrobial arsenal and spread rampantly in the community.[15]

The normal gut microbiota that otherwise maintains the immune functions is also targeted by antibiotic spectrum. Drug-resistant bacterial infections entail higher doses of drugs, with augmented toxicity, longer hospital stays and enhanced mortality. Thus, antimicrobial resistance remains a substantial global health concern, invigorating the critical need for alternate therapeutic options to combat chronic intracellular infections and biofilms so as to shorten the hospital stays, and hence mortality.

Drug resistance subterfuge evolved by bacteria

The acquisition of resistance to single and multiple antibiotics by bacteria (Figure 1B) has been reported to occur through horizontal gene transfer on plasmids or transposons by transformation, conjugation and transduction or by spontaneously mutating the existing genes.[18] The resistance becomes rampant due to selective pressure for microbes expressing resistance genes against the antimicrobial drug, created by overuse of antibiotics, non-patient compliance or use of time-dependent drugs with long half-lives or microbiostatic drugs.[7] Modes of resistance mechanisms[19] that endanger the efficacy of antibiotic arsenal are summed up as follows.

Active antimicrobial drug efflux and reduced uptake

Drug efflux pumps preclude the entry of drugs or extrude the antibacterial agent from the microbial cell before it

reaches its target site to exert its effect. Overexpression of transmembrane multidrug efflux pumps as well as reduced uptake results in sub-toxic levels of drugs within the microbial cells.[20] In *P. aeruginosa*, mutation in regulatory protein that normally dampens the gene encoding efflux proteins results in enhanced outpour. *E. coli* uses transmembrane proton gradient to expel multiple antibiotics through its numerous efflux pumps. The increased drug resistance of Gram-positive bacteria is also attributed to the outer membrane surrounding the periplasmic space that restrains the uptake of hydrophobic drugs. The antibiotic uptake or efflux may also be affected by mutations such as the diminished expression or absence of porins in *P. aeruginosa*, lowering the permeability of the cell wall to carbapenems.[21] In case of both Gram-positive and Gram-negative bacteria, one of the genes encoding tetracycline efflux pumps (TetA) is normally not expressed due to TetR repressor protein. However, tetracycline binds to and inactivates TetR, thereby inducing TetA expression that catalyzes drug efflux.[7]

Expression of resistance gene encoding altered substrate

The antibacterial agent has diminished affinity for the resistance gene-encoded altered antibiotic target sites on the substrate than the wild-type site. This is exemplified in case of penicillin-resistant *Streptococcus pneumoniae* (due to MecA gene conferring resistance to all β-lactams), vancomycin-resistant *S. aureus* and vancomycin-resistant *Enterococcus* (due to VanA resistance gene), sulfonamide-resistant *S. pneumoniae*, *Streptococcus pyogenes*, *Neisseria* spp. and *E. coli*.[7] This mechanism also accounts for conferring resistance against aminoglycosides, macrolides, β-lactams, sulfonamides, linezolid, tetracyclines, rifampin and quinolones.[7,22] Resistance genes coding for enzymes that methylate 23S rRNA of the 50S ribosomal subunit and 16S rRNA of the 30S ribosomal subunit inhibit binding by macrolides (such as erythromycin) and aminoglycosides, respectively.[7,23]

Covalent modification of antimicrobial drug, dampening its efficacy

Plasmids or transposons and rarely bacterial chromosomes harbor resistance genes encoding aminoglycoside-modifying enzymes that covalently alter the OH or NH_2 groups on aminoglycosides, thereby undermining their affinity for 30S ribosomal subunit, and waning their antimicrobial activity. β-Lactamases, having broad-spectrum activity against most of the β-lactam antibiotics, including cephalosporins, have evolved by gene transfer.[5,21] Chloramphenicol acetyltransferases modify chloramphenicol, making it unable to bind to 50S ribosomal subunit and inhibit protein synthesis. Covalent modification also affords resistance against tobramycin, gentamycin, chloramphenicol, kanamycin, macrolides, tetracyclines, quinolones and streptogramins.[7,23]

Synthesis of a competitive inhibitor of antibiotic

S. aureus and *Neisseria meningitidis* acquire sulfonamide resistance by producing its inhibitor (para-aminobenzoic acid) that competes for binding the active site of bacterial dihydropteroate synthetase.[7,24] Mutations in this enzyme have also been found in many clinical isolates, downgrading sulfonamide-based therapies to second- or third-line options.

Biofilm formation to avoid contact with antibiotics

Biofilms are surface-adherent aggregates of bacterial communities embedded within an extracellular, self-produced, polymeric matrix. Intracellular bacteria in biofilms have limited exposure to antibiotics. Biofilms also act as a barrier of diffusion by trapping and degrading antibiotics and thus render tolerance to even high concentrations of antibiotics, a phenomenon called recalcitrance, resulting in recurrent or chronic bacterial infections as with *S. aureus* and *P. aeruginosa*.[15] Biofilms can also favor gene transfer between bacteria, thus spreading antibiotic resistance and transforming a previously non-virulent commensal into a virulent pathogen.[25]

Nanotechnology-based therapeutic interventions to fight nosocomial pathogens

Several metals, metal oxides, metal halides and bimetals in nanoparticulate form have been documented for antimicrobial activity[5,26] as the bacteria are less likely to develop resistance to nanomaterials. These comprise NPs containing Ag, Au, Zn, Cu, Ti, Mg, Ni, Ce, Se, Al, Cd, Y, Pd and superparamagnetic Fe. Zerovalent bismuth-containing NPs have shown promise in treating infections due to drug-resistant bacteria in combination with X-rays.[27] Among the metal-containing NPs, Au NPs have moderate antibacterial activity unless their surface is modified. Ag NPs are the most effective nano-weapon against bacterial infections.[28–30] On the other hand, upsurge in resistance to Ag NPs has been reported due to genetic alterations in bacteria.[31] The deposition of silver

of Ag NPs in the liver, spleen, lungs and other organs results in organ damage and dysfunction, and seriously erodes its efficacy. Al_2O_3 NPs promote horizontal conjugative transfer of MDR genes, increasing antibiotic resistance.[32] The high toxicity of CuO NPs causes oxidative lesions, while DNA damage induced by ZnO and TiO_2 NPs limits the efficacy of these NPs. Nonetheless, NPs have emerged as alternative antimicrobial approach to combat biofilms and for treating severe bacterial infections.[33] The NPs-mediated elimination of the microbes may be microbicidal, or the effect may be microbiostatic, wherein the growth of bacteria is arrested and metabolic activities are ceased and the killing is potentiated by the host's immune cells.

Mode of action of metal-based nanomaterials

Metallic NPs use multifaceted contrivance simultaneously to combat microbes (Figure 2), depreciating the probability of development of resistance, as it would entail multiple concurrent gene mutations in the same microbe for evolvement of that resistance. The molecular mechanisms by which metal-based NPs annihilate MDR bacteria, resulting in disturbance in respiration and inhibition of cellular growth, have been extensively reviewed.[28,29,33] Table 1 summarizes the metallic NPs that have been reported for antibacterial activity via an array of mechanisms enlisted as follows.

ROS generation

The toxicity of nanomaterials has been attributed to ROS production such as hydroxyl radicals, superoxide anions and hydrogen peroxide that inhibit DNA replication as well as amino acid synthesis and damage the bacterial cell membranes via lipid peroxidation, compromising membrane semipermeability and repressing oxidative phosphorylation. Hydroxyl radical (•OH) formation has been observed with Ag NPs[28,29,34] and hydrogen peroxide (H_2O_2) with ZnO NPs,[35] while TiO_2 NPs[36] produce both via photocatalysis. Free Cu^{++} from Cu-containing NPs[37] and Mg halogen (MgX_2)-containing NPs[38] also induce formation of ROS.

Release of metal ions and disorganization of bacterial membrane

Different microorganisms have varying sensitivities to metal ions. Ag and ZnO NPs have been reported to exert antibacterial activity by release of Ag^+ and Zn^{++} that disrupt the membrane.[28,29,35,39] The antibacterial action of Ag NPs is revealed by interaction of Ag^+ with sulfhydryl groups in enzymes and other cellular constituents, making them

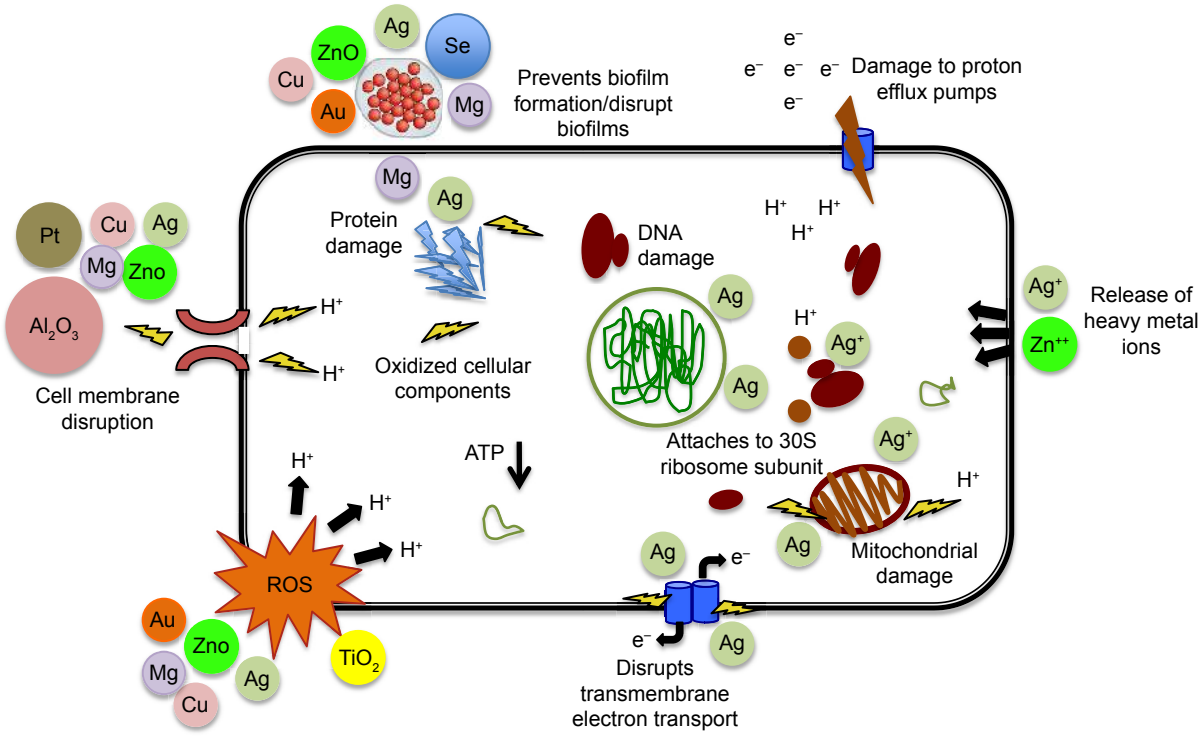

Figure 2 Probable nanomaterials-based bactericidal effects. Nanomaterials trigger release of heavy metal ions that intercalate between bases, damage cellular proteins, disrupt cell signaling, generate free radicals and prevent biofilm formation.
Abbreviation: ROS, reactive oxygen species.

Table 1 Metallic nanomaterials-based probable bactericidal effects

NPs	Target bacteria	Microbicidal effects	References
Ag	*Acinetobacter baumannii*, *Salmonella typhi*, *Vibrio cholerae*, *Bacillus subtilis*, *Staphylococcus aureus*, MDR *Escherichia coli*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, coagulase-negative *Staphylococcus epidermis*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *Proteus mirabilis*, *Micrococcus luteus*	ROS generation, lipid peroxidation, inhibition of cytochromes of ETC, bacterial membrane disintegration, inhibition of cell wall synthesis, increase in membrane permeability, dissipation of proton gradient resulting in lysis, adhesion to cell surface causing lipid and protein damage, ribosome destabilization, intercalation between DNA bases, disruption of biofilms	28,30,39,52
Au	*E. coli*, *S. aureus*, *B. subtilis*, *K. pneumoniae*	Loss of membrane potential, disruption of respiratory chain, reduced ATPase activity, decline in subunit of ribosome for tRNA binding, bacterial membrane disruption	41,43
ZnO	*S. aureus*, *E. coli*, *P. aeruginosa*, *B. subtilis*, *Stenotrophomonas acidaminiphila*	ROS generation, inhibition of biofilm, Zn^{2+} release, enhanced membrane permeability	35,46
	Methicillin-resistant *Streptococcus agalactiae*, MRSA	ROS production, disruption of membrane, adsorption to cell surface, lipids and protein damage, inhibition of microbial biofilm formation	35
	Enterobacter aerogenes, *E. coli*, *Klebsiella oxytoca*, *S. aureus*, *S. pyogenes*	Cell membrane interaction	53
Cu	*B. subtilis*	ROS generation, disorganization of membrane, inhibition of DNA replication	40
	E. coli	Dissipation of cell membrane potential, ROS generation, lipid peroxidation, protein oxidation, DNA degradation	37
Se	*S. aureus*, *E. coli*	Biofilm inhibition	49
TiO_2	*E. coli, P. aeruginosa*, *S. aureus*, *Enterococcus faecium*	ROS generation, adsorption to cell surface, inhibition of biofilm	36,45
NiO	*S. aureus*, *Streptococcus pneumoniae*	Increase in bacterial cell wall permeability	44
CdS	*E. coli*	Antibiofilm activity	50
YF_2	*E. coli*, *S. aureus*	Antibiofilm properties	48
MgF_2	*E. coli*, *S. aureus*	ROS generation, penetration of cell envelope, lipid peroxidation, biofilm inhibition	38
MgO NP with Cl_2 and Br_2	*E. coli*, *Bacillus megaterium*, *B. subtilis*	Adsorption on cell membrane	54
Bi NP	*Streptococcus mutans*	Inhibition of biofilm	27
Bi NPs with X-ray treatment	MDR *P. aeruginosa*	Free radical generation that damages bacterial DNA	42
Al_2O_3 NPs	*E. coli*	Cell wall damage, enters cytoplasm	32
Ag/Cu bimetallic NPs	*E. coli*	Synergistic effect	55
Cu/Zn bimetal NPs	*E. coli*, *S. aureus*, MRSA	Antioxidant activity	56
Ce-doped TiO_2 NPs	*E. coli*	Membrane damage, penetration of cell envelope	47
Ag NPs impregnated with TiO_2 films	*E. coli*, *S. pyogenes*, *S. aureus*, *A. baumannii*	ROS production	36
Superparamagnetic iron oxide NPs coated with Ag or Au	*E. coli*, *S. aureus*, *P. aeruginosa*, *E. faecalis*, *S. epidermidis*	Inhibition of bacterial biofilms	51

Abbreviations: NPs, nanoparticles; MDR, multidrug resistant; ROS, reactive oxygen species; ETC, electron transport chain; MRSA, methicillin-resistant *Staphylococcus aureus*.

dysfunctional. Ag^+ also precludes cell wall synthesis in Gram-positive bacteria. Cu^{++} interacts with amine and carboxyl groups on the surfaces of microbial cells, such as *Bacillus subtilis*.[40] Au NPs also result in bacterial membrane disruption.

Intercalation between DNA bases

Ag^+ released from NPs has also been reported to interact with DNA of microbes,[28,29] and inhibit DNA replication and cell division. Inhibition of DNA replication and DNA degradation has also been reported with Cu NPs.[37,40] Bi NPs in combination with X-ray treatment emit electrons, with formation of free radicals that damage bacterial DNA.[48]

Adsorption of nanomaterials to bacterial cell

The electrostatic interaction between the NPs and the microbial cells affects its toxicity, with the positively charged NPs being more toxic as has been observed with TiO_2 and surface-modified Au NPs.[36,41] The NPs adsorption to the surface of

bacteria results in oxidative stress due to redox reactions, leading to toxicity. The adhesion of Ag and ZnO NPs to bacterial cell surface also results in damage to membrane lipids and proteins.[28,29,35]

Alteration in bacterial membrane permeability

Cell surface adherence of Ag and polyvinyl alcohol (PVA)-coated ZnO NPs coupled with ROS generation increases membrane permeability and triggers cell death.[28,29,35] The membrane viscosity is also altered, influencing the transport across the membrane. Ag^+ released from Ag NPs interacts with negatively charged lipopolysaccharide in the bacterial membrane, permeabilizing it and dissipating the electrochemical proton gradient across the membrane, resulting in lysis.[7] Ag^+ inhibits cytochromes of the electron transport chain, and disrupt cellular transport systems by causing homeostatic imbalance due to K^+ loss from the membrane. Loss of membrane potential and disruption of respiratory chain has also been observed with Au,[43] Cu[37] and NiO NPs.[44]

Penetration of the cell envelope and ribosome destabilization

The NP surface charge also affects the internalization and subcellular localization and hence toxicity as with $CeCl_2$ NPs.[45] Entering of NPs into the cytoplasm to exert microbicidal effects via oxidative stress has been observed with Ag nanomaterials[28,29] and PVA-coated ZnO NPs.[35] MgF_2 NPs cause lipid peroxidation and enter the membrane of microbial cells, causing a fall in cytoplasmic pH, which raises the membrane potential.[38] Al_2O_3 NPs cause oxidative damage to membrane and enter cytoplasm.[32] Ag and Au NPs have been reported to exert toxicity by penetrating inside the cell and denaturing 30S ribosomal subunit, thereby impeding protein translation.[29,30,41]

Disruption of bacterial biofilms

During bacterial biofilm maturation, the extracellular matrix (slime) and extracellular carbohydrates known as quorum sensing molecules (for cell-to-cell communication) are produced.[46] The slow-growing bacterial cells detach, resulting in spread of infection. Ag[28,29] and ZnO NPs[47] are also documented to inhibit the microbial biofilm formation. YF_2[48] and Se NPs[49] restrain growth and biofilm formation of *E. coli* and *S. aureus*. TiO_2,[36] CdS,[50] MgF_2[38] and Bi NPs[27] have also been reported to disrupt bacterial biofilms. Magnetic NPs such as superparamagnetic iron oxide NPs coated with Ag or Au exhibit the greatest activity against bacterial biofilms.[39,51]

Antibacterial activities of ecofriendly green NPs

The potentiality of prokaryotes and plants to reduce inorganic metals has advanced a stimulating, cost-effective strategy towards the NPs synthesis via green nanotechnology.[57] Plant- as well as microbe-mediated metallic NPs synthesis (bottom-up or biological method) avoids the generation of toxic by-products, and is hence ecofriendly and a green alternative to conventional methods (top-down or physical methods and bottom-up or chemical methods) for mining nanomaterials.[58] The biologically synthesized metallic NPs are biocompatible and potentially safe for human therapeutic use. A plethora of literature highlights the antimicrobial activities of biogenic metallic NPs (Table 2). *Rosmarinus officinalis* leaf extract-mediated green synthesis of Ag NPs has been reported to have remarkable activity against *B. subtilis*, *E. coli*, *P. aeruginosa* and *S. aureus*,[59] while biogenic Ag NPs from *Ficus benghalensis* and *Acalypha indica* demonstrated antibacterial potential against *B. subtilis*, *E. coli*, *P. aeruginosa* and *Vibrio cholerae*.[60] Ag NPs synthesized using leaves extract of *Skimmia laureola*,[61] root extract of *Delphinium denudatum*,[62] *Styrax benzoin* extract[63] and *Rosa chinensis* flower extract[64] showed potent antibacterial effects against a spectrum of Gram-positive and Gram-negative human pathogenic bacteria. Ag NPs synthesized using *Caesalpinia sappan* extract served as a potential novel nanoantibiotic against MRSA.[65] Biologically synthesized Ag NPs using *Coffea arabica* seed extract have been found to exhibit significant antibacterial activity against *E. coli* and *S. aureus*, that was almost equivalent to that elicited with the standard drug ampicillin.[66] Inhibitory activity of green synthesized ZnO NPs from *Solanum nigrum*,[67] CeO_2 NPs from *Olea europaea* leaf extract,[68] and Fe_3O_4-Ag core shell magnetic NPs obtained using *Vitis vinifera* stem extract[69] against both Gram-positive and Gram-negative pathogens has also been reported. The antibacterial activities of biologically synthesized NPs are due to the metal ions released from the NPs, coupled with the bio-organic compounds used in the green synthesis that may interact with the microbial membrane as well as preclude the need for reducing and stabilizing agent.[70] However, the biosynthetic NPs have not been found to surpass the non-biosynthetic NPs in antibacterial effects or vice versa.

Immunomodulatory effects of nanomaterials based on metals

Metal-based NPs are known to trigger innate as well as adaptive immune responses.[86] The immunostimulatory

Table 2 Antibacterial activities of green NPs

Green synthesized NPs	Target bacteria	Antibacterial effects	References
Ag NPs from *Phyllanthus amarus* extract	MDR *Pseudomonas aeruginosa*	Membrane damage, release of free ions, inactivation of enzymes by interaction with thiol groups	71
Ag NPs from *Helicteres isora* fruit extract	Extensively drug-resistant (XDR) *P. aeruginosa* isolates	Lipid peroxidation, leakage of reducing sugars and proteins, respiratory chain dehydrogenases inactivation, turbulence of membrane permeability	72
Ag NPs from *Artemisia cappilaris* extract	Methicillin-resistant *Staphylococcus aureus*	Membrane damage, release of free ions	73
Ag NPs from aloe vera extract	*Staphylococcus epidermidis*, *P. aeruginosa*	Release of free ions, increase in membrane permeability, ROS production, DNA damage	70
Ag NPs from *Acalypha indica* leaf extracts	*Escherichia coli*, *Vibrio cholerae*	Alteration in membrane permeability and respiratory chain	74
Ag NPs from *Rhizopus oryzae*	*E. coli*, *P. aeruginosa*	ROS production, membrane damage, alteration in membrane permeability	75
Ag NPs from extracts of *Cocus nucifera* influorescence	*Vibrio alginolyticus*, *Klebsiella pneumoniae*, *P. aeruginosa*, *Bacillus subtilis*, *Plesiomonas shigelloides*	Interference with the molecular build-up of bacterial cell wall	76
Ag, Zn NPs extracted from *Caltropis procera* fruits or leaves	*V. cholerae*, *E. coli*	Inhibition of adenyl cyclase, restraining biofilm formation	77
Au NPs from *Citrullus lanatus* rind	*Bacillus cereus*, *E. coli*, *Listeria monocytogenes*, *S. aureus*, *Salmonella typhi*	Antioxidant activities	78
Ag, Au, Ag–Au bimetallic NPs extracted from *Plumbago zeylanica*	*E. coli*, *Acinetobacter baumannii*, *S. aureus*	Biofilm inhibition	79
Ag, Au and Ag/Au bimetallic NPs using *Gloriosa superba* leaf extract	*S. aureus*, *Streptococcus pneumoniae*, *K. pneumoniae*, *E. coli*	Antibiofilm activities	80
Ni NPs from *Ocimum sanctum* leaf extract	*E. coli*, *K. pneumoniae*, *S. typhi*, *B. subtilis*, *S. epidermidis*	ROS production, release of free ions, membrane damage, inhibition of electron transport	81
Al_2O_3 NPs from leaf extract of lemongrass	MDR *P. aeruginosa*	Intracellular oxidative stress contributing to loss of cell membrane integrity	82
Pd NPs using agroforest waste *Moringa oleifera*	*Enterococcus faecalis*, *B. cereus*, *S. aureus*, *E. coli*	Antioxidant activity	83
Se NPs from *Bacillus licheniformis*	*B. cereus*, *E. faecalis*, *S. aureus*, *E. coli*, *S. typhi*, *Salmonella enteritidis*, *S. aureus*	Antibiofilm activity	84,85

Abbreviations: NPs, nanoparticles; MDR, multidrug resistant; ROS, reactive oxygen species.

potential of Ag, CeO_2 and surface-modified Au NPs has been reported.[87] Immunostimulatory NPs may serve as double-edged swords by acting on bacteria as biocidal nanoweapons, as well as undermining the bacterial resistance to host immunity. ZnO NPs increased interferon gamma, TNF-α and IL-12 expression in primary human immune cells,[88] while in another study, IL-6, IL-1β, IL-8 and TNF-α were induced by ZnO NPs from peripheral blood mononuclear cells.[53] TiO_2[89] and SiO_2 NPs[90] activated inflammasomes and induced IL-1β release, which affected fibroblast proliferation. Ag NPs also induced inflammasome formation and triggered IL-1β release and subsequent caspase-1 activation.[91] Size-dependent immunomodulatory effect of Au NPs has been reported that may inhibit IL-12p70 production by DCs and Th2 polarization, or promote Th17 potentiation.[92] CeO_2 NPs stimulated IL-10 production from DCs and triggered a strong Th2-biased cytokine profile. On the contrary, TiO_2 NPs induced DCs to release IL-12 and polarize T cells to a Th1-bias.[93] TiO_2 NPs and nanoplatinum triggered proinflammatory cytokine production, DC maturation and näive T cell activation and proliferation.[94,95] A benign ε-polylysine/Ag nanocomposite has been reported to modulate the relative levels of $CD3^+$ T cells and $CD68^+$ macrophages and promote infected wound healing.[96]

Synergistic antibacterial effects of nanomaterials with antibiotics or alternate antimicrobial compounds

While most metal-based NPs are microbicidal to an array of bacteria, genetic alterations in bacteria may result in rapid evolution of resistance to Ag NPs,[31] whereas Al_2O_3 NPs trigger increased expression of conjugation-promoting genes, thus promoting horizontal transfer of antibiotic resistance genes. NPs have been tailored to subdue resistance

by packaging multifarious antimicrobial agents, resulting in development of resistance, which is a subtle possibility since it would require multiple simultaneous gene mutations in the same bacteria.[97,98]

The functionalization of NPs using antibiotics (Table 3) is not only a promising nanoplatform to combat bacterial resistance but may also reduce the dose and hence toxicity of the drugs. NPs target or deliver antimicrobial agents to the infected site, thereby overcoming resistance as well as mitigating their hazardous impact on normal cells. Synergistic antibacterial efficiency of Ag NPs and antibiotics has been observed against *S. aureus*, *E. coli* and *P. aeruginosa* at extremely low concentrations.[99] The efficacy of ampicillin coupled with Ag NPs was identical in Gram-positive and Gram-negative bacteria, unlike the difficulty in inhibition of Gram-positive bacteria with Ag NPs alone.[39] Green synthesized NPs may also be used as an antibiotic adjuvant for the treatment of various bacterial infections (Table 3). Ag NPs boost the antimicrobial effects of several antibiotics, including penicillin G, amoxicillin, vancomycin, clindamycin and erythromycin against *S. aureus*, *E. coli* and MDR bacteria.[100] The antibiotic-functionalized NPs may promote reversal of antimicrobial resistance.

Combinatorial effect of Ag NPs with natural alternative compounds such as cinnamaldehyde[117] and eugenol[118] has also been reported. Se NPs conjugated with quercetin and

Table 3 Drug–nanomaterial synergy for antibacterial therapy

Nanomaterials	Antibiotics	Affected bacteria	References
Ag NPs	Chloramphenicol	*Salmonella typhi*	101
		Enterococcus faecium, *Pseudomonas aeruginosa*	102
	Polymyxin B, rifampicin	*Acinetobacter baumannii*	103
	Vancomycin	*Enterobacter aerogenes*	39
	Ampicillin	MRSA, *P. aeruginosa*, *E. aerogenes*, *Escherichia coli*	104
		E. coli, *E. faecium*, *Streptococcus mutans*, *Staphylococcus aureus*, *P. aeruginosa*	102
	Ciprofloxacin	VRE	105
	Vancomycin	VRE, *E. coli*	
	Vancomycin	MRSA	106
	Clotrimazole	MRSA, *S. aureus*	107
Ag NPs plus blue light	Amoxicillin, azithromycin, clarithromycin, linezolid	MRSA	108
γ-Cyclodextrin-capped Ag NPs	Chloramphenicol	*P. aeruginosa*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *S. aureus*	109
Au NPs	Ampicillin	MRSA, *P. aeruginosa*, *E. aerogenes*, *E. coli*	104
	Vancomycin	VRE, *E. coli*	110
	Vancomycin	MRSA	106
	Kanamycin	*Streptococcus bovis*, *Staphylococcus epidermidis*, *E. aerogenes*, *P. aeruginosa, Yersinia pestis*	111
	Streptomycin, gentamycin, neomycin	*S. aureus*, *Micrococcus luteus*, *E. coli*, *P. aeruginosa*	54
ZnO NPs	Ciprofloxacin, ceftazidime	MDR *A. baumannii*	112
	Ciprofloxacin, erythromycin, methicillin, vancomycin	*E. faecalis*, *E. faecium*	105
Ag NPs from leaf extract of *Typha angustifolia*	Gentamicin, cefotaxime, meropenem	*E. coli*, *K. pneumoniae*	113
Ag NPs from *Acinetobacter calcoaceticus*	Vancomycin	*E. aerogenes*	114
	β-Lactam antibiotics	MDR *A. baumannii*, vancomycin-resistant *S. mutans*	
Ag NPs from *E. coli*	Bacitracin	*E. coli*, *Salmonella paratyphi* B	58
	Ampicillin	*Corynebacterium diphtheriae*	
	Kanamycin	*K. pneumoniae*	
	Gentamycin	*P. aeruginosa*	
	Bacitracin, gentamycin, erythromycin, ciprofloxacin	*S. aureus*	
Citrate-capped Ag NPs from *Allium sativum*	Cephalothin, cefazolin, chloramphenicol	*M. luteus*, *Bacillus subtilis*, *P. aeruginosa*, *E. coli*	115
Au NPs from *Adiantum philippense* extract	Amoxicillin	MRSA	116
Au NPs from *Citrullus lanatus* rind	Kanamycin, rifampicin	*Bacillus cereus*, *E. coli*, *Listeria monocytogenes*, *S. aureus*, *S. typhi*	78

Abbreviations: NPs, nanoparticles; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; MDR, multidrug resistant.

acetylcholine had synergistic effect against MRSA, causing irreversible membrane damage.[119] Resveratrol nanocarriers with Au NPs and Ag NPs had potent activity against Gram-positive and Gram-negative bacteria.[120] The combination of biologically synthesized Ag NPs (produced by *Fusarium oxysporum*) and oregano (*Origanum vulgare*) essential oil showed bactericidal effects against non-methicillin-resistant *S. aureus* (non-MRSA) and β-lactamase- and carbapenemase-producing *E. coli* and *A. baumannii* strains.[121] *Nigella sativa* essential oil-synthesized Au NPs effectively inhibited the biofilm formation of *S. aureus* and *Vibrio harveyi*.[122]

Polymeric nanocomposites and nanomaterials conjugated with antibodies and other ligands and drug–NP complex for targeted delivery

Antimicrobial NPs can be easily trapped within polymer films to form lipid–polymer hybrid NPs or nanocomposites. Enhanced biocompatibility and stability coupled with controlled release make these superior alternatives to metallic NPs. Synergistic antibacterial effects of some polymers and metal nanomaterials have been identified. The biocidal activities of Ag and Cu NPs embedded in polymer matrices have been reported to be enhanced due to release of metal ions while dampening their toxicities.[55,123] Ag nanocomposites have been reported to be biocidal against MRSA.[124] A benign ε-polylysine/Ag nanocomposite demonstrated antibacterial effects against *P. aeruginosa* and *S. aureus* that was mediated by surface adherence, irreversible disruption of the membrane with subsequent penetration and inhibition of protein activity, ultimately leading to bacterial apoptosis.[96] Low-density polyethylene-containing ZnO nanocomposites have been found to be effective against *B. subtilis* and *Enterobacter aerogenes*.[125] Ag/Fe_3O_4 nanocomposites demonstrated high antibacterial activity against *E. coli*[126] and graphene-oxide Ag nanocomposites against MRSA.[127]

Targeted NP delivery to the infection site could also be achieved by surface modification with ligands or antibodies, which may further improve therapeutic efficacy and reduce the side effects of antimicrobial drugs. The effectiveness of Ag NPs is also augmented with compounds such as polyethyleneimines, chitosan and glucosamine that serve as ligands and reinforce their uptake into bacterial cells.[128] Chitosan has inherent antimicrobial properties due its polycationic character. Low-molecular weight chitosan-coated Ag NPs have been reported to surpass polyvinylpyrrolidone-coated Ag NPs and Ag NPs without surface stabilizer (uncoated Ag NPs) in efficacy against MRSA with enhanced biocompatibility and reduced body absorption characteristics.[129] Chitosan/TiO_2/Ag nanocomposites exhibited effective antibacterial activity via ROS generation, lactate dehydrogenase release and inhibited bacterial adhesion.[130] Chitosan/Ag nanocomposites were effective against *Salmonella* sp.,[131] whereas the activity of chitosan-TiO_2:Cu nanocomposite against *E. coli* and *S. aureus* was enhanced in the presence of light.[132] Chitosan/calcium silicate nanocomposites doped with Ag^+ exhibited antibacterial activity against *S. aureus* and *P. aeruginosa*.[133] Ag NPs capped with lipoic acid were effective against *Staphylococcus epidermidis* and *Streptococcus mutans* biofilm.[134] Ag-decorated poly (DL-lactide-co-glycolide) NPs exhibited high efficacy against *S. epidermidis* biofilms.[135] Biodegradable lignin-core NPs coated with cationic polyelectrolytes and infused with Ag^+ exhibited broad-spectrum biocidal activity against Gram-positive as well as Gram-negative bacteria at lower concentrations of Ag^+ than the conventional Ag NPs and hence suggested as greener alternatives to Ag NPs.[136] Antibacterial (*P. aeruginosa*) activity of iron oxide NPs was also enhanced upon chitosan coating.[137] Superior antibacterial activity of UV-irradiated glucosamine-functionalized Au NPs on graphene oxide against *E. coli* and *Enterococcus faecalis* has been reported that was better than kanamycin.[138] Gallic acid-capped Au NPs have been found to be effective against both Gram-positive and Gram-negative bacteria.[139] Synthetic peptides (containing arginine, tryptophan and cysteine termini)-immobilized Au NPs exhibited targeting capacity and activity against *Staphylococci*, *Enterococci* and antibiotic-resistant bacterial strains.[140] Microbial (*Ochrobactrum rhizosphaerae*) glycolipoprotein-capped Ag NPs exhibited antibacterial activity against *V. cholerae* comparable to ciprofloxacin.[141] Besides the targeting ligands, NPs conjugated with antibodies against surface antigen of the target microbe such as anti-protein A antibodies have been shown to have high selectivity for killing *S. aureus*. Conjugating Bi NPs to antibodies against the target has been found to be effective against MDR *P. aeruginosa* when irradiated with low-dose X-rays.[54] Similarly, the IgG in IgG-Fe_3O_4@TiO_2 magnetic NPs has been shown to target *S. pyogenes*.[54]

Drug–NP complex represents another type of polymeric NPs that are highly attractive as drug delivery vehicles due to their stability, ease of functionalization and sustained release. These may be made multifunctional by incorporating different polymers. Chitosan-functionalized Au NPs adsorbed on vancomycin-encapsulated liposomes released the antibiotic

in the presence of anti-toxin antibody secreted by *S. aureus*, inhibiting its growth.[142] Lipids like phosphatidylinositol and stearylamine presented specific affinity with biofilms, thereby increasing the biofilm adhesion of liposomes. Anti-biofilm activities of phosphatidylcholine-decorated Au NPs loaded with gentamycin have been reported against *P. aeruginosa*, *S. aureus* as well as intracellular *Listeria monocytogenes* and *E. coli*.[143] NP-based drug delivery could subjugate systemic toxic effects of antibiotics, decrease uptake and increase efflux of drugs, biofilm formation and intracellular bacterial infection.

Conclusion and perspectives

Bacteria are increasingly dodging extermination as they have evolved innate immune resistance strategies. Antibiotics remain the mainstay to fight bacterial infections, but episodes of resistant infections are alarmingly on the rise. The indiscriminate use of antimicrobial agents in the community, hospital and agriculture is undeniably responsible for fuelling this crisis. This also causes selective pressure, allowing only the fittest genotype to thrive, resulting in emergence of MDR bacterial strains, and emphasizing the need for surrogate therapeutic options. The emergence of resistant and more virulent strains of bacteria has outpaced the development of new antibiotics over the last few decades. NPs are now being considered as a viable alternative to antibiotics due to their biocidal and immunopotentiating properties. The polymer-based nanomaterials and metal NPs may also be exploited as antimicrobial coatings on surface of medical devices for various biomedical applications. Metallic NPs when used with the existing antibiotics for bacterial infections lower the antibiotics dosage to be administered, thereby minimizing toxicity as well as reducing the probability of development of resistance. There has been a paradigm shift towards cost-effective and ecofriendly green synthesis of antibacterial NPs. This approach holds promise alone or synergistically with antibiotics targeting various bacterial infections, paving way for future therapeutics in nanomedicine. This combinatorial approach may serve as adjunct to the existing therapies and may help to restrain the escalating nosocomial threats. However, their translation to clinics would entail an in-depth understanding of the pharmacokinetics and biodistribution of NPs.

Disclosure

The author reports no conflicts of interest in this work.

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