



Mode of Action of Biogenic Silver, Zinc, Copper, Titanium and Cobalt Nanoparticles Against Antibiotics Resistant Pathogens

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Abstract

The rapid surge in antibiotic resistance to pathogens has emerged as a grave threat to public health, globally. This multiple drug resistance (MDR) is directly linked to the high rates of morbidity and mortality worldwide due to untreated microbial infections. Therefore, it is inevitable to identify some novel, efficient, and comparatively safer antimicrobial agents to rescue the declining health index. In this regard, nanomaterials with modified structure, size, and infinity have risen as the sole source to tackle the MDR either through ameliorating the efficacy of existing drugs or by triggering entirely new bactericidal mechanisms. Out of all the nanomaterials, metals, and metal oxide nanoparticles with biopolymer-induced reduction have fetched the attention of global researchers due to their significant and promising pathogen-killing ability without any hint of resistance. The current review covers the updated molecular modes of resistance development in Gram-positive and Gram-negative bacteria, comprehensively. This review also highlighted the detailed mode of action of various metallic nanoparticles (silver, zinc, copper, titanium, and cobalt) against MDR pathogens. Moreover, this review article thoroughly discussed the correlation between the mechanisms of resistance and alternative NPs bactericidal modes for better understanding for the readers. Last but not least, toxicity analysis is also explained for safe further use.

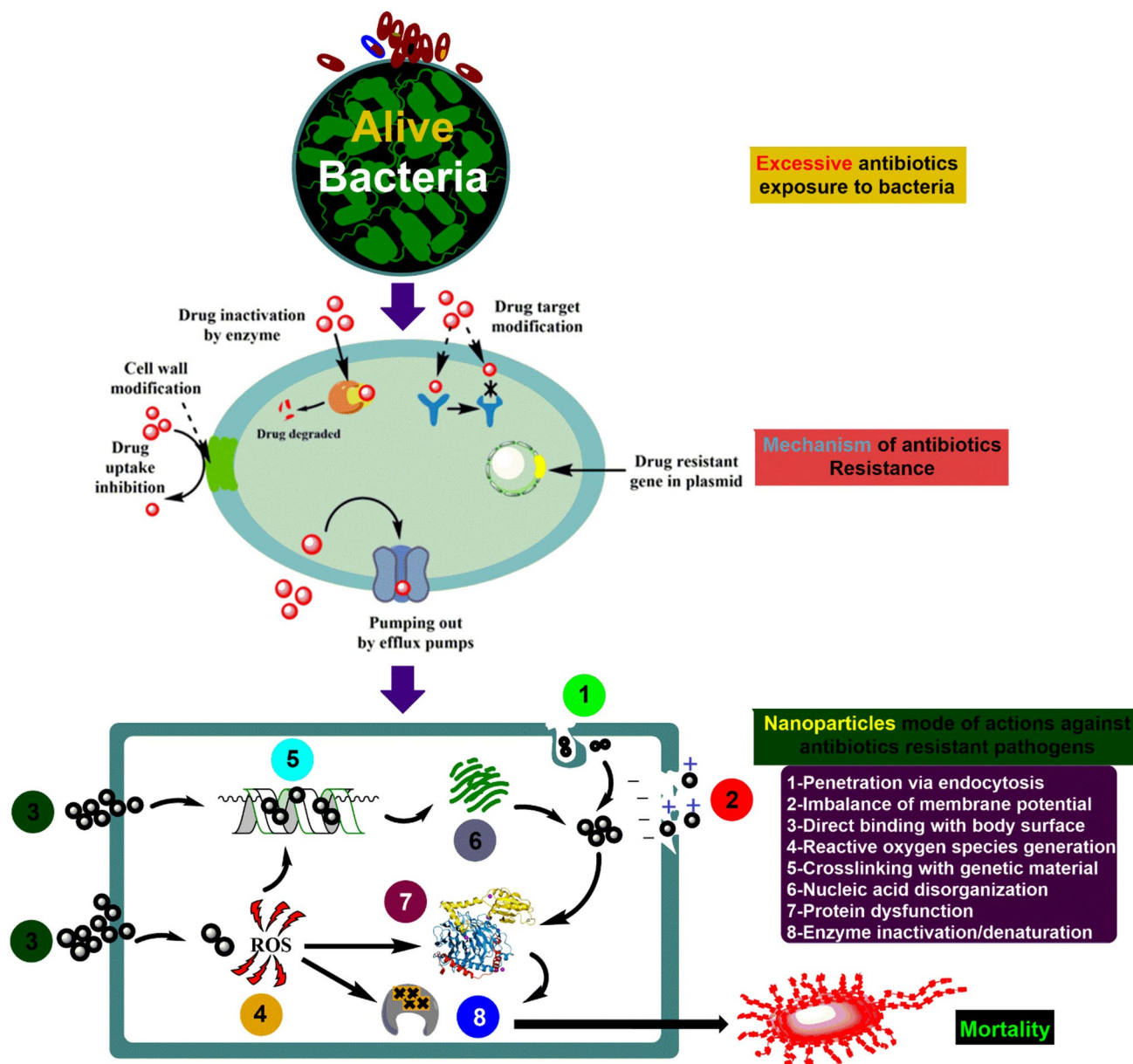
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Graphical Abstract



Keywords Antibiotic · MDR · Nanoparticles · Mode · Pathogens

1 Introduction

Bacterial adherence, proliferation, and infections have become momentous and consequential health and economic problems in everyday life [1–3]. This grave issue is posing serious threats to several growing industries like medicine, textile, food packaging, and marine transport, globally [4–6]. Antibiotics are fundamental in defense against bacterial infections and were thought of as a magic bullet that would selectively target the disease-causing microbes

without affecting the host [7–9]. However, there is a continuous decrease in the remedial potential of existing antibiotics. Although antibiotic resistance is a natural response by bacteria, it is greatly accelerated due to its unregulated, over and misuse, leading to the emergence of multiple drug resistance (MDR) [10–13]: [14–17]. Antibacterial resistance is also bacteria's natural response to the selective pressure of an antibiotic. Due to this, a drug is unable to control bacterial growth effectively and they continue to reproduce even in the presence of therapeutic levels of antibiotics [18–20].

Microbial resistance against multiple antibiotics is posing serious concerns to the human health index which can significantly contribute to prolonged hospital stays and affect the ratio of mortality and morbidity as a consequence of bacterial diseases [21–23].

It is claimed that a post-antibiotic era is imminent due to the speeded evolution of bacterial resistance and a diminished antibiotic pipeline. This would result in common infections being untreatable that were previously fixable [24–26]. It is reported that infections caused by MDR bacteria could result in 10 million deaths per year by 2050. This would not only influence the economy dreadfully but could also push 24 million people into extreme poverty by 2030 [27]. Further, the emergence of MDR endorses the concept of innovation, supervision of consumption, and a swift decrease in the misuse of antibiotics [28–31].

In the dilemma of resistant superbugs, nanoparticles have emerged as the sole hope to tackle the grave issue. Nanoparticles being prepared from chemical and natural

reducing agents have been in action against pathogenic bacteria [32]. However, the chemically synthesized NPs pose several indirect and direct toxicological threats due to their chemical origin [33]. On the contrary, biosynthesized NPs got a global interest in various biomedical fields due to the incorporation of biocompatible and biodegradable reducing agents like bacteria, fungi, phytochemicals, and proteins, etc. [14–16, 34]: [35]: [14–16, 36]. Moreover, the application of chemically fabricated NPs is now discouraged due to their high cost, more time to synthesize, and less biocompatibility [37].

This review will explain the various mechanisms of antibiotic resistance acquisition by the bacteria. It will also narrate the various classes of antibiotics and their route for resistance (Fig. 1). Furthermore, it briefly explains the use of different nanomaterials as potential antimicrobial agents and their modes of action. Last but not least, the toxicity perspective of the biogenic NPs is also narrated in this review.

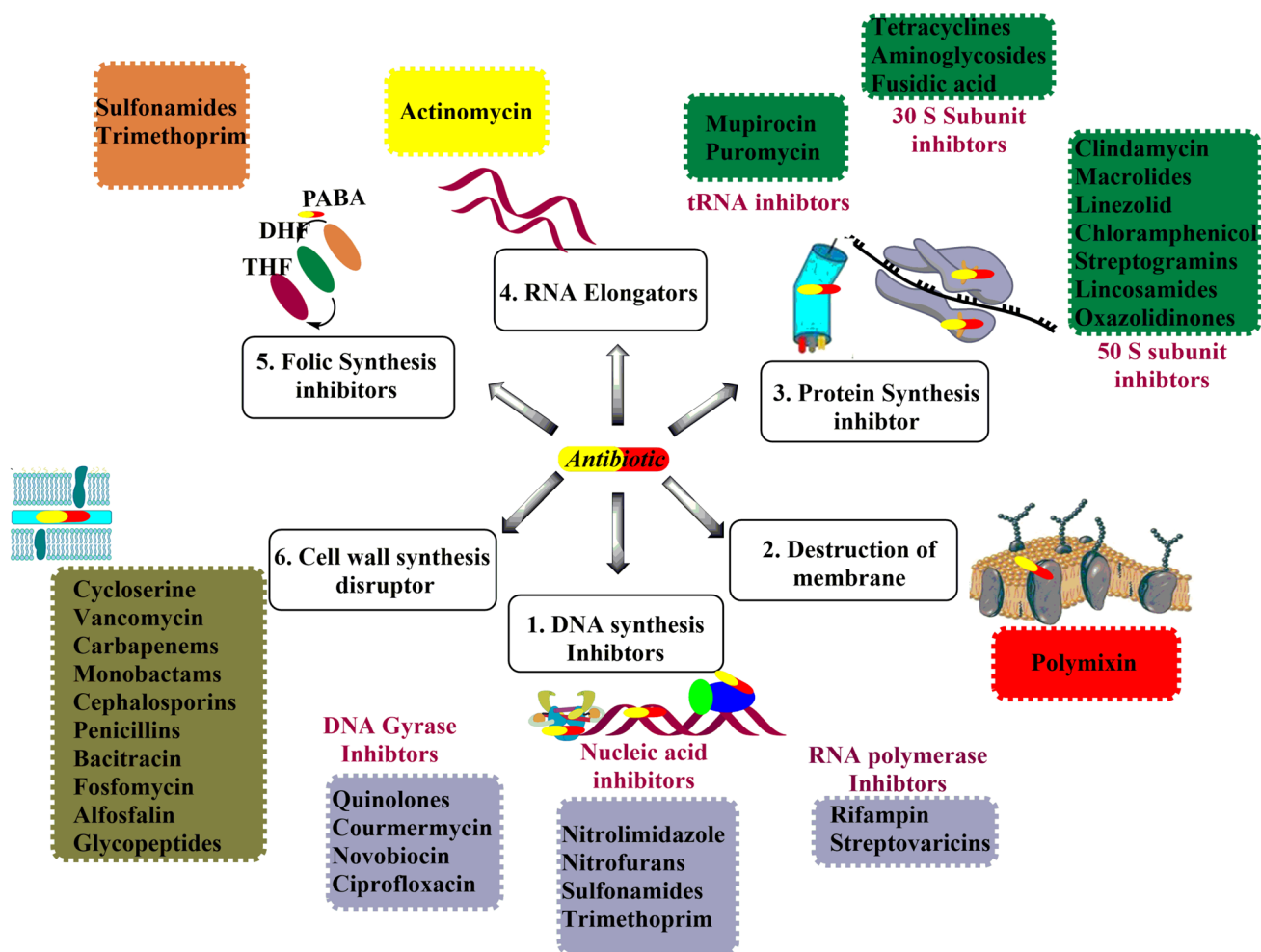


Fig. 1 Different classes of antibiotics and their mode of actions

2 Types of Drug Resistance

There are three possible forms of drug resistance exhibited by bacteria that provide them with advantageous modifications to survive in hostile conditions [38–40].

2.1 Intrinsic Resistance

Natural or intrinsic resistance is associated with a change in the structural properties of bacterium. These are inherent characteristics and are not linked to antibiotic selective pressure. For example, the change in permeability of the outer membrane in Gram-negative bacteria makes them insusceptible to glycopeptides [41–43]. Other intrinsic antibiotic resistance mechanisms include up-regulation of efflux pumps, activation of drug-altering enzymes, and change in the target site of the antibiotic [43, 44] (Fig. 3).

2.2 Acquired Resistance

Acquired resistance emerges when previously susceptible bacteria gain resistance by alteration in their genetic material. Extrinsic antibiotic resistance mechanisms include mutation in existing genetic features, genetic rearrangement, or acquiring exogenous genetic material through transformation, transduction, and conjugation as shown in Fig. 2 [45–47]. Horizontal gene transfer (HGT) is the chief method responsible for the sharing of antibiotic resistance genes between bacteria which has been reportedly increasing due to ongoing antibiotic abuse [48, 49].

2.3 Adaptive Resistance

Adaptive resistance is exhibited as a result of epigenetic changes caused by certain environmental signals e.g., pH, stress, growth rate, levels of antibiotics, and ion concentrations (Fig. 3). However, adaptive resistance is transient and bacteria revert to the non-resistant phenotype, once the external stimulus is removed [39, 40, 50, 51].

3 Mechanisms of Antibiotic Resistance

The major mechanisms of antibiotic resistance include antibiotic inactivation, target site alterations, removal of the drug by active efflux pump, change in a metabolic pathway, alteration of bacterial membrane permeability, and biofilm formation through quorum sensing.

3.1 Antibiotic Inactivation

Enzymatic inactivation of drugs by certain bacteria is an important mechanism for antibiotic resistance. They release

drug-degrading enzymes that add an acetyl or phosphate group to the site of the antibiotic, decreasing its ability to attach to the ribosome and causing disruption in protein synthesis [52–54]. Genes encoding enzymes may be an intrinsic part of bacterial genome or can also be attained via HGT. Penicillin-resistant bacteria produce the most known enzymes called β -lactamases. They destroy the β -lactam ring of antimicrobial drugs having antimicrobial properties [55, 56]. This type of resistance mechanism has been reported in both Gram-positive and Gram-negative bacteria [57].

3.2 Target Site Alteration

The efficacy of the antibiotic drug depends on its interaction with the target site. To minimize the antibiotic effect of the drug, bacteria modify the target proteins thus affecting the antibiotic-protein interactions [56, 58]. Certain bacteria produce ribosomal protection proteins (RPPs) that bind to the bacterial ribosome resulting in conformational changes in ribosomes. This change in the shape of ribosomes prevents the binding of the antibiotic and the bacteria's protein-synthesizing machinery remains unaffected [59–61]. A well-known example of target site alterations is the mutation in the penicillin-binding proteins (PBPs) in *Streptococcus pneumoniae* leading to resistance against β -lactam antibiotics [62].

3.3 Active Efflux Pumps

Efflux pumps are responsible for expelling the solutes/toxins from inside of the cell. These energy-dependent efflux pumps are present on the plasma membrane and prevent the accumulation of antibiotics by pumping the drug outside the cell and maintaining the internal environment [63–66]. Resistance against the tetracycline group of antibiotics is developed via antibiotic efflux systems [65, 67, 68].

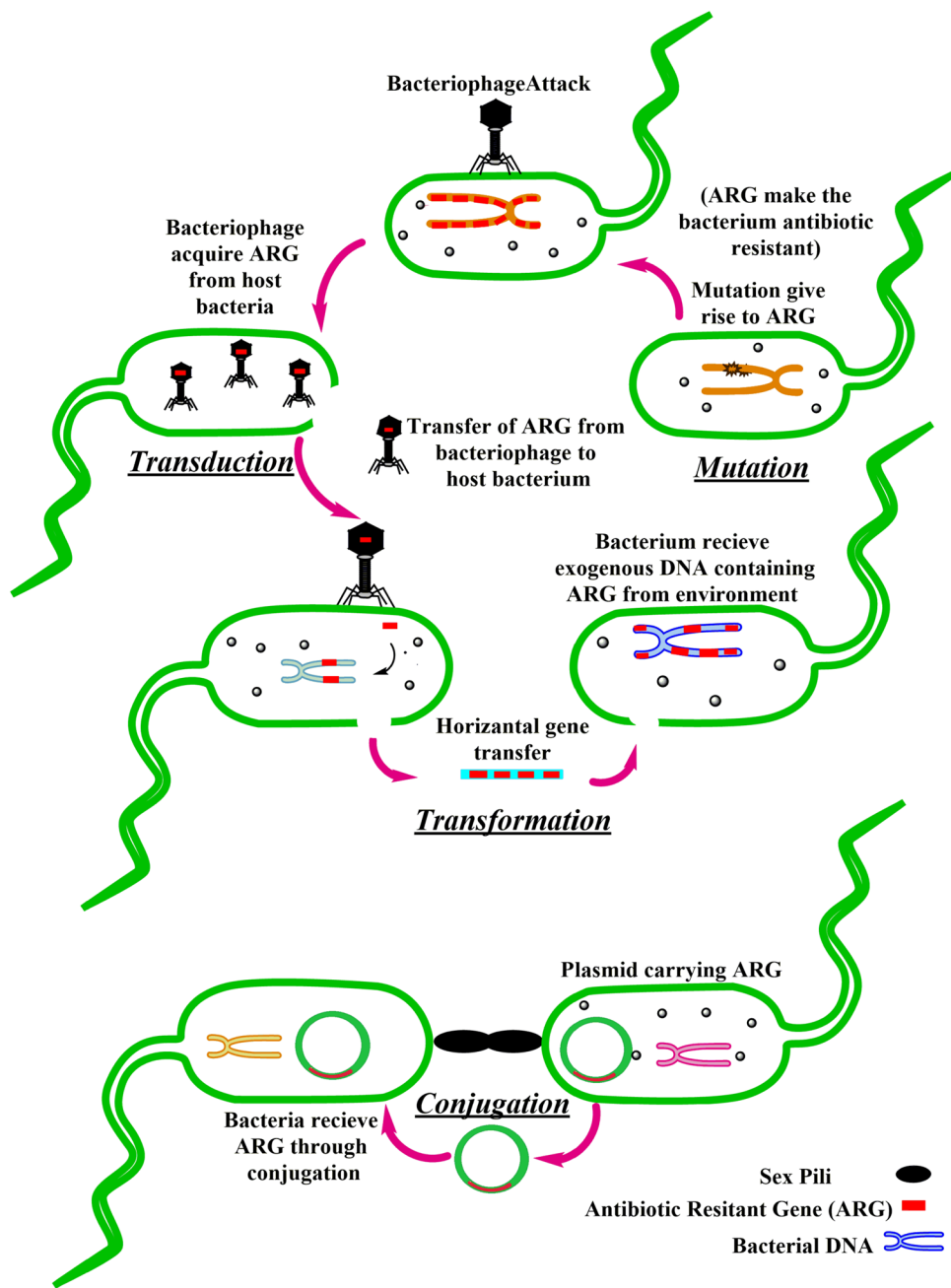
3.4 Changing the Metabolic Pathway

Certain bacteria overcome the drug effect by altering the metabolic pathway. For example, bacteria become resistant to sulfonamides by changing the metabolic pathway for the synthesis of folic acid. They synthesize folic acid from the environment instead of synthesizing it from Para-aminobenzoic acid (PABA), a precursor involved in folic acid synthesis which is inhibited by sulfonamides [69, 70].

3.5 Alteration of Bacterial Membrane Permeability

Change in the permeability of the internal and external membrane of bacterial cells results in decreased drug uptake. [71, 72]. Transporting proteins and channels i.e.,

Fig. 2 Mechanism of acquired resistance



porins in the bacteria’s outer membrane are a major entry route for hydrophilic antibiotics. Change in the number and type of porins in the membrane via mutation in specific porins called OprD, affects the susceptibility of bacteria for the antibiotics such as carbapenems, quinolones, and β -lactams [72–74]. Gram-negative bacteria are more resistant to antibiotic drugs as compared to Gram-positive bacteria. The reason lies in the complex outer wall architecture making them more likely to use a reduced permeability mechanism [73, 75] (Fig. 4).

3.6 Biofilm Formation Through Quorum Sensing

In an aqueous environment, certain bacteria build a network of extracellular polymeric substances (EPS). This mainly comprises of polysaccharides, proteins, DNA, and lipids that develop a shielding matrix around them and facilitate their attachment to a solid substrate [76]. Due to the extracellular network and metabolic dormancy, microorganisms covered in the biofilm are difficult to eliminate because it becomes practically more impossible for antibiotics to enter the multi-layer structure as compared to a single cell (without biofilm/

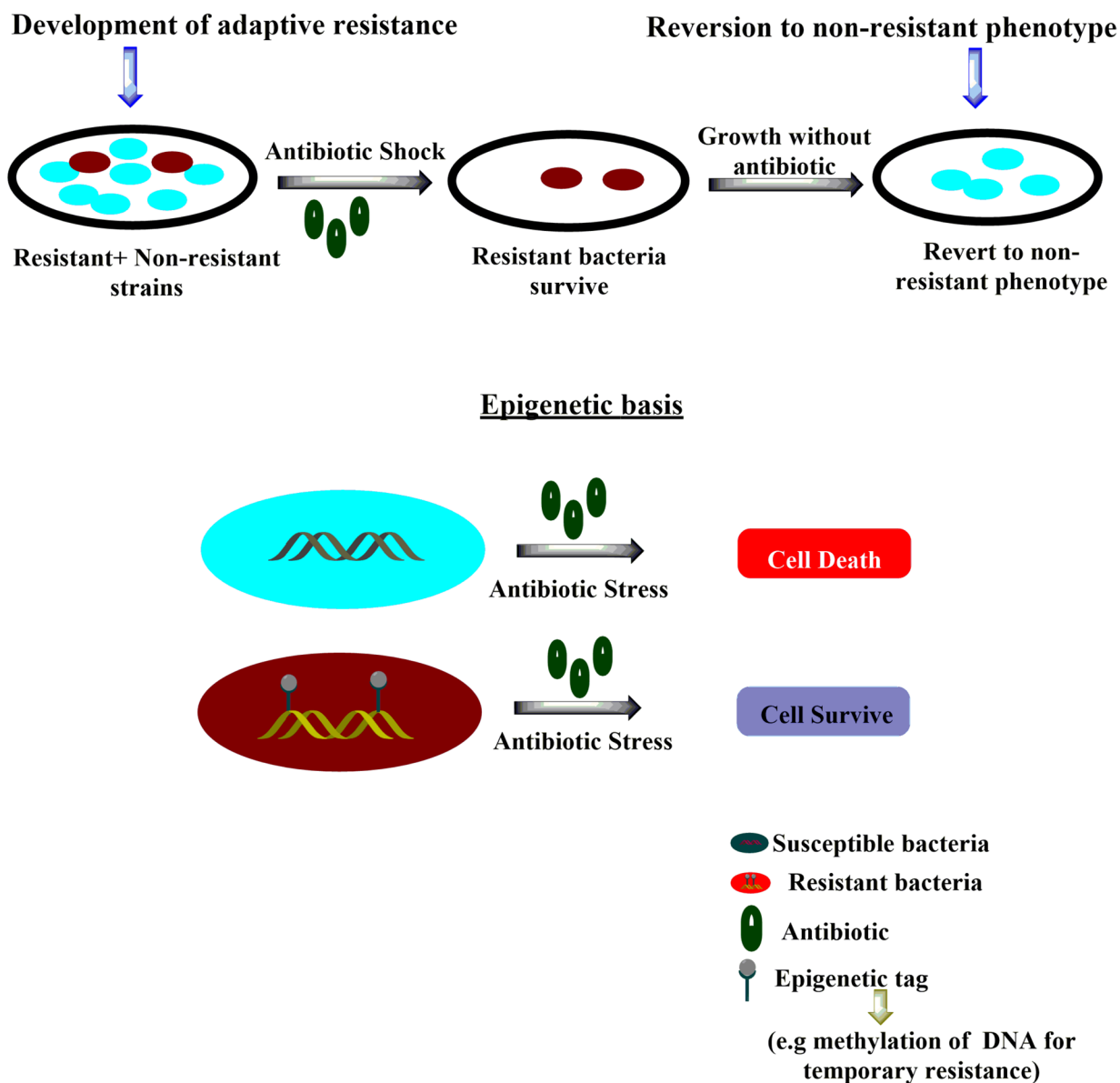


Fig. 3 Mechanism of adaptive resistance

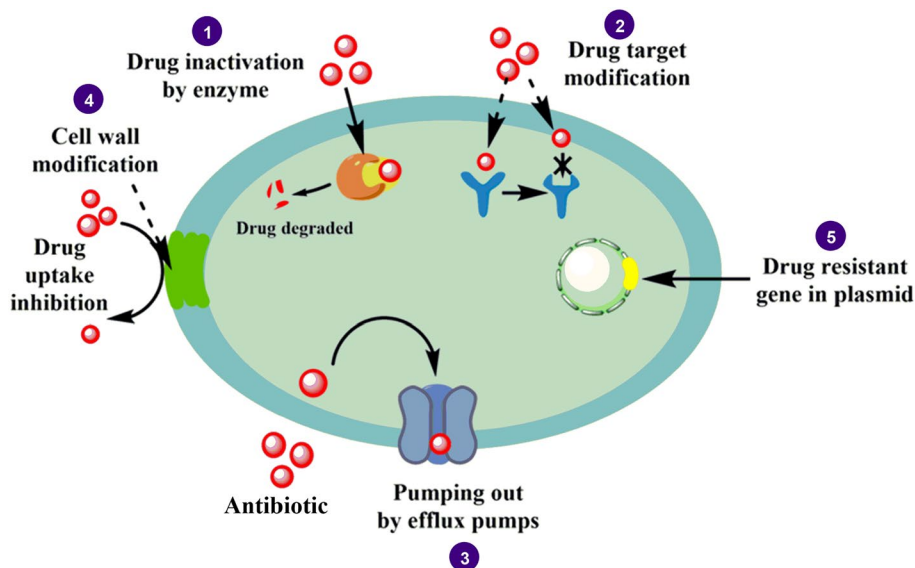
microcolonies) [77, 78]. It also helps them cling to solid surfaces and acquire a multicellular lifestyle by multiplying inside biofilms which leads to the formation of microcolonies, which are then enclosed in a layer of hydrogel that serves as a barrier between the microbial population and the outside world [79].

Hence, biofilm helps them to infect the host, spread into a new substratum as well as defend them against stress in their environment such as desiccation, high temperature, and action of antibiotics [80–83]. As a result, bacterial species often establish a resistance to conventional medications by adapting to these challenges [84]. Furthermore, biofilms give rise to the antibiotic degrading enzyme and increase communication between bacteria which makes it easier for

mutations to occur by facilitating the transmission of genetic material, which also leads to antibiotic resistance [80–83].

There are multiple processes involved in the formation of the biofilm, including adherence, cell-to-cell binding, growth, maturity, and dispersion [85]. A signaling pathway known as the quorum sensing (QS) pathway is involved in the development of a coordinated functional community inside a biofilm [86]. It is used by bacteria to communicate with one another within their community through chemical signals called autoinducers. These autoinducers released by one bacterium are also detected by others in a community. When the amount of these molecules reaches a threshold concentration (a quorum), it binds to receptors present in bacteria. The target bacterium subsequently undergoes

Fig. 4 Modes of development of antibiotic resistance



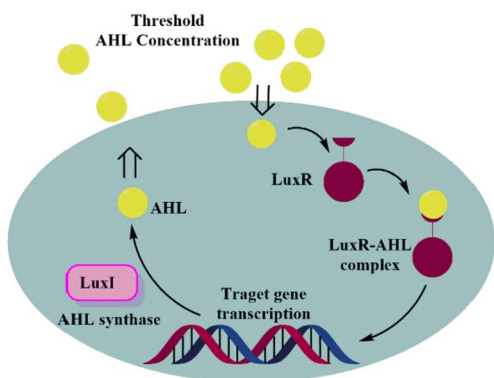
transduction of the signal into an intracellular biochemical signal and experiences changed gene expression [87]. This auto-signaling system induces cellular processes such as food uptake, movement, exchange of genetic material, and production of secondary metabolites as well as physiological responses such as activation of biofilm formation, and production of antibiotics degrading enzymes [88].

Biofilms contribute to antibiotic resistance by decreased antibiotic penetration due to its hampered diffusion across EPS; an anaerobic environment in inner layers and increased protection due to differentiation and specialization of the bacterial cell [89]. There are three primary QS systems including acyl homoserine lactone QS system (AHL), auto-inducing peptide (AIP) QS system and the autoinducer-2 (AI-2) system [90] as explained in Fig. 5.

3.6.1 Quorum Sensing in Gram-Negative Bacteria

3.6.1.1 Acyl Homoserine Lactone (AHL) QS System It is also termed as “LuxI/LuxRtype” quorum sensing. LuxI is an AHL synthase that synthesizes Acylated homoserine lactones (AHL) from fatty acid [91]. AHLs are autoinducers primarily released by Gram-negative bacteria. This inducing molecule enters bacterial cells and binds LuxR forming LuxR-AHL complex in bacterial cell cytoplasm. luxR (AHL-dependent transcription regulatory protein) undergoes conformational changes and exposes its DNA binding site. This activated protein binds target gene on DNA and transcribes it [92]. There exists a different homolog of LuxI/LuxR signaling system in Gram-negative bacteria. For example, LasI/LasR-RhlI/RhlR virulence system in *Pseu-*

Acyl homoserine lactone (AHL) QS system (Gram-negative bacteria)



Autoinducing peptide (AIP) QS system (Gram-positive bacteria)

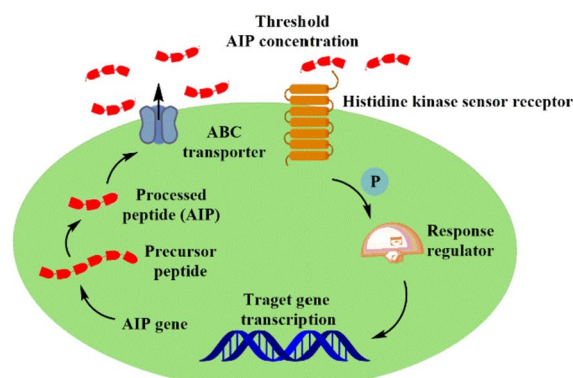


Fig. 5 Mechanism of antibiotic resistance through biofilm formation by quorum sensing

domonas aeruginosa, TraI/TraR Virulence System in *Agrobacterium tumefaciens*, ExpI/ExpR-CarI/CarR Virulence System in *Erwinia carotovora* and LuxI/LuxR Bioluminescence System in *Vibrio fischeri* [80–83].

3.6.2 Quorum Sensing in Gram-Positive Bacteria

3.6.2.1 Autoinducing Peptide (AIP) QS System Gram-positive bacteria release AIP autoinducer signal for quorum sensing [93]. These are amino acids or processed oligopeptides that are cleaved, modified and transported through ABC (ATP binding cassette) transporter. When the secreted peptide (AIP) reaches threshold concentration, it binds to cell membrane-bounded histidine kinase sensor receptor and phosphorylates it. This phosphoryl group is subsequently transferred to response regulator protein which activates and binds to DNA and causes transcription of QS target gene [94]. Homologs of AIP QS system signaling system in Gram-positive bacteria include ComD/ComE, Competence System in *Streptococcus pneumoniae*, ComP/ComA Competence System in *Bacillus subtilis* and AgrC/AgrA Virulence System in *Staphylococcus aureus* [95].

3.7 Resistance Development Variations in Gram-Positive and Gram-Negative Bacteria

3.7.1 Resistance Mechanisms in Gram-Negative Bacteria

Pseudomonas aeruginosa develops resistance against carbapenem and imipenem by porin mutations causing OprD porin deficiency, overexpression of hydrolyzing enzymes such as AmpC, and increased levels of efflux pumps like MexCD-OprJ and alteration of PBPs, which decreases sensitivity to β -lactams and acquire drug degrading enzymes such as β -lactamases and Class B carbapenemases [96]. Macrolide, tetracyclines, and TMP/SMX resistance are similarly regulated by efflux pump production [97]. Its ability to resist colistin is based on altering the negative charge of the outer membrane essential for binding with the positively charged antibiotic. This is accomplished by the production of N4-aminoarabinose, a molecular compound that bind to, and consequently neutralizes the negative charge of lipid A. Moreover, mutations in the RNA polymerase gene cause rifampicin resistance in it [98].

E. coli strains develop resistance by synthesizing a wide range of β -lactamases, particularly AmpC, ESBLs, and class A, B, and D carbapenemases (OXA-48 & NDM) [99]. Furthermore, *Enterobacteriaceae* and *E. coli* develop resistance against fluoroquinolones, macrolides, rifampicin, and tetracyclines in a similar fashion [100]. Target site alteration using methylases, macrolide inactivation by phosphotransferases or esterases, and the development of efflux pumps are all modes of development of macrolide resistance and

rpoB gene mutations cause Rifampicin resistance [101, 102]. Fluoroquinolone resistance is mainly brought about by polymorphisms of one nucleotide in *gyrA* gene, whereas tetracycline resistance is mediated by the overproduction of efflux pumps expressed by *tet* genes and the downregulation of porin [103].

Klebsiella pneumoniae become resistant to penicillins like ampicillin by synthesizing β -lactamases like TEM-1 and SHV-1. Carbapenemases that develop resistance in *K. pneumoniae* include Ambler Class A, VIM, IMP and NDM of Ambler Class B, Ambler Class D OXA-48 [104]. It acquired resistance against cephalosporins by production of AmpC, ESBLs and wide spectrum β -lactamases [105]. It develops resistance against aminoglycosides by producing efflux pumps, aminoglycoside altering enzymes that acetylate, adenylate or phosphorylate the target antibiotic, or by producing 16S rRNA methylase, which prevents aminoglycoside binding to 30S ribosomal subunit [106]. Fluoroquinolone resistance pathways include mutations in target enzyme *gyrA* gene, overexpression of *acrAB* efflux pump, possesses *qnr* genes on a plasmid, which encode proteins that protects DNA gyrase and topoisomerase IV from fluoroquinolones [107]. Tetracycline resistance is primarily caused by the development of efflux pumps like TetB [108]. Tigecycline resistance arises by upregulation of *acrAB* efflux pump, which develops either by a lack of inhibition of RamA, its transcription activator, or by disabling mutations in *AcrR* transcriptional repressor [109]. It also has ability to form biofilms which render antibiotics ineffective [110].

Acinetobacter baumannii acquire resistance through Class B carbapenemases like IMP and VIM, changes in PBPs and porins which give significant degrees of carbapenem resistance [111]. Tetracycline resistance arises by the synthesis of RPPs (ribosomal protection proteins) or the expression of TetA and TetB efflux pumps [112]. Resistance against tigecycline is linked to the expression of the AdeABC efflux pump or decreased uptake by mutations in *plsC* gene encoding integral membrane protein needed for tigecycline permeability [113]. *A. baumannii* develops resistance to aminoglycosides by producing all forms of aminoglycoside-altering enzymes, particularly nucleotidyltransferases, aminoglycoside, acetyltransferases and phosphotransferases [114].

Fluoroquinolone resistance is achieved through mutations in the genes encoding topoisomerase IV and DNA gyrase which reduce their susceptibility to fluoroquinolones and by the development of *qnr*-type protective proteins, which prevent fluoroquinolone binding to DNA gyrase and topoisomerase IV [115]. Furthermore, *A. baumannii* can also overexpress efflux pumps and inhibit the production of porins, lowering fluoroquinolone intracellular concentrations. The AdeABC efflux pump imparts resistance to many antibiotics simultaneously, including

carbapenems, cephalosporins, fluoroquinolones, and aminoglycosides [116].

3.7.2 Resistance Mechanisms in Gram-Positive Bacteria

Gram-positive bacteria can develop resistance through two major mechanisms: the enzyme-mediated degradation of antibiotics through β -lactamases, or by decreasing the receptivity of target site i.e., penicillin-binding protein (PBP). It is done either by acquiring exogenous genetic material or by alterations in PBP genes [117]. VISA (Vancomycin intermediate *Staphylococcus aureus*) and VRSA (Vancomycin-resistant *S. aureus*) develop antibiotic resistance through cell wall modification. VISA resistance was associated with D-Ala-D-Ala residues in thicker cell wall than susceptible counterparts that serve as deceptive targets, preventing vancomycin from reaching its actual targets.

VRSA acquires resistant vanA gene containing plasmid from *Enterococcus faecalis*. It substitutes normal D-alanyl-D-alanine terminal with D-alanyl-D-lactate terminal that decreases binding affinity of vancomycin leading to antibiotic resistance [118]. *S. aureus* develop resistance to methicillin and β -lactam antibiotics by acquiring resistant gene from heterologous sources that code for PBP2a for which antibiotics have lowest affinity [119].

S. aureus give rise to penicillinase encoded by plasmid, which disintegrates penicillin's β -lactam ring, which is crucial for its antibacterial effect and to become penicillin resistant [120]. Resistance to ciprofloxacin, fluoroquinolones in *S. aureus* evolved as a result of mutations in genes encoding specific enzymes required for DNA replication i.e., DNA gyrase subunit gyrB and Topoisomerase IV subunit grIA, as well as alterations in drug entry and increased number of NorA efflux pump [121, 122]. *S. aureus* acquire resistance against linezolid via variety of mechanisms such as single nucleotide mutations in its binding site V domain of 23S rRNA, inactivating methyltransferase that methylate 23S rRNA and mutations in L3 protein of 50S ribosomal subunit which comes in contact with ribosomal peptidyl transferase [123]. Tetracycline resistance in *S. aureus* is achieved by ribosomal protection proteins, which dislodge drug from its binding site ribosome, or by developing efflux pumps [124].

Resistance to penicillin in *Streptococcus pneumoniae* develops as a result of changes in at least one of the six PBPs in cell membrane of *S. pneumoniae*. This may have arisen by chromosomal mutation or acquired from other bacteria through transformation [125]. Resistance against lincosamide-macrolide-streptogramin in *S. pneumoniae* is caused by the erm(B) gene, which encodes a methylase, or by the mef(A) gene, which produces an efflux pump [126]. It has been documented that *S. epidermidis* becomes methicillin quinolones and vancomycin-resistant

as a result of the transfer of the resistant mecA gene, which encodes PBP2a [127]. *Streptococcus viridans* serve as carriers for resistance genes like mel and mef(E) and established resistance to penicillin and other β -lactam antibiotics due to a modification in the penicillin-binding protein [128].

High resistance levels of *E. faecium* to fluoroquinolones have been documented and is developed by point mutations in parC and gyrA gene which encode topoisomerase IV A and DNA gyrase subunit A and NorA efflux pump [129]. Single nucleotide mutations in the S12 ribosomal protein of *E. faecium* lead to high-level streptomycin resistance [130]. *E. faecium* and *E. faecalis* become resistant to aminoglycosides by making their cell walls impermeable to aminoglycosides. *E. faecium* synthesizes phosphotransferases and acetyltransferases to disable aminoglycosides enzymatically, including kanamycin, tobramycin and amikacin [131]. Resistance to gentamycin in *Enterococcus faecalis* is achieved by enzymes that acetylate and phosphorylate the antibiotic, rendering it impossible to bind its target. Rifampicin resistance in both *E. faecalis* and *E. faecium* arises through mutations in rpoB gene encoding RNA polymerase [132].

Streptococcus agalactiae resistance to erythromycin and other macrolides is caused by either structural modification in ribosome expressed by erm genes or efflux pump encoded by mefA genes. Furthermore, in *Streptococcus agalactiae*, ribosomal translocation expressed by linB genes resulted in clindamycin resistance [133]. *Bacillus anthracis* and *Bacillus cereus* develop resistance against cephalosporins, ampicillin, penicillin and trimethoprim by producing β -lactamases [134]. *Corynebacterium diphtheria* becomes resistant to sulfonamides, chloramphenicol and tetracyclines by acquiring resistant genes such as sul1, tet(W) and cmx via horizontal gene transfer [135]. Resistance to fluoroquinolones and tetracyclines emerged in *Listeria monocytogenes* by acquiring highly active efflux pump and conjugative transposons, respectively [136].

4 Role of Nanoparticles

To address the escalating problem of antibiotic resistance, there is an urgent need to modulate or even replace the current protocols of using drugs that could assist in lowering drug dependency (DD) [137–141]. Therefore, the search for novel and effective strategies regarding the control of bacterial damages is an urgent exigency and has become a priority for researchers worldwide [4, 6, 142–144]. Recently, nanoparticles (NPs) have emerged as promising tools to combat antibiotic resistance of human pathogens against antimicrobial agents [145–150]. These varieties of NPs could also be conjugated with various phytochemicals to enhance their respective biomedical potentials [80–83]. The antimicrobial

properties of NPs are attributed to their smaller size and larger surface area to volume ratio which provides greater surface area for NPs contact with microbes [151, 152].

Nanoparticles are known to kill bacteria mainly by the physical rupture of the cell membrane, damaging the intracellular components via Reactive Oxygen Species (ROS) generation and by suppressing the bacterial metabolism [14–16, 110, 153, 154].

4.1 Antimicrobial Potential of Silver Nanoparticles (AgNPs)

Silver has been known to old civilizations for its medical-based applications for 2000 years [155]. Since the beginning of the nineteenth century, different compounds retaining silver as a major component have been in use for various antimicrobial purposes [156, 157]. Moreover, it is a fact that silver compounds are toxic to different types of microbes [158–160]. Nanoparticles composed of silver are also categorized as potent and viable antimicrobials against a broad spectrum of bacteria including MDR species due to multiple modes of action and high penetration potential [4, 161, 162]. Different properties like the high surface-to-volume ratio of AgNPs make them a more suitable and efficacious antibacterial agent than their counterparts [163–166]. As a result of this particular factor, AgNPs expressed specific chemical, physical and biological characteristics [167]. On the other hand, the stability of silver nanocomposites is a major concern, which makes its role in the medical and health sector, debatable [4, 168].

In this regard, AgNPs are now being synthesized in different environmental conditions (temperature, light) to assess their stability [169]. Second, human and eco-related toxicity of AgNPs has also emerged as it causes mitochondrial mutilation [170]. To overcome the problem of cytotoxicity, alternative eco-friendly stabilizing and reducing agents like different biopolymers are being used [171–173]. Tahir et al. [150] also reported the synthesis and antibacterial activity of AgNPs by using sericin (biopolymer) as a reducing and stabilizing agent. Many other phytochemicals including terpenoids, phenols like eugenol, bacterial probiotics, fungi, algae, proteins, oils and their secondary metabolites have the reducing ability for NPs synthesis as well as individual antimicrobial potential.

4.1.1 Mode of Action of AgNPs

Many scientists have published across the world various mechanisms by which these metallic NPs work against a wide variety of bacteria. Lazar [174] and Periasamy et al. [175] observed and disclosed that the cell membrane deterioration leading to the structural mutations ultimately causes the death of different bacteria when exposed to the AgNPs.

Multiple studies against *E. coli* revealed that AgNPs accumulation in the cell creates gaps in the membranes leading to stability loss and thus microbes collapse [176–178]. The efficiency of NPs is inversely dependent upon their size i.e., smaller the size, the greater the penetrance into the bacterial cell and the higher the mortality and vice versa as depicted by several studies conducted by Collins et al. [179], Wu et al. [180], Tamayo et al. [181], Franci et al. [167], Chen et al. [182] and Muchintala et al. [183]. It seems that when NPs with positive potential come into contact with a bacterial surface with a negative charge, attract each other and NPs enter the cell [182].

It is also evident from the studies that resistance against silver is very rare which indicates the multiple and collective microbe-killing mode of actions [184, 185]. Different studies conducted by Rolim et al. [186], Beyth et al. [187] and Lee & Jun, [173] revealed that free radicals are generated when reactive oxygen species are produced by the interaction of bacterial cells with silver-based nanocomposites, causing the mortality. Bury et al. [188], Morones et al. [189] Jung et al. [190], Lee & Jun, [173] and Muchintala et al. [183] revealed that AgNPs can also cause the blockade of protein synthesis and mRNA movement in the cell leading to the genetical collapse depicted in Fig. 6.

Moreover, NPs are responsible formation of free radicals which finally disrupt the membrane potential and bacterial cell lost integrity [191–194]. It is revealed by recent studies conducted by Elgorban et al. [195] and Shaban et al. [196] that activities of AgNPs i.e., smaller NPs ranging from 1 to 10 nm efficiently damage the membrane and cause respiratory problems than their bulk counterparts. Narware et al. [197] reported that AgNPs kill the bacteria through the oligodynamic mode of action i.e., by inactivation of respiratory enzymes.

4.1.2 Bacterial Strains and Nanoparticles Mode of Action

4.1.2.1 Nanoparticle's Mode of Action Against Gram-Positive Bacteria There are non-significant differences in the bactericidal mode of the various NPs against Gram-positive and Gram-negative pathogens [198]. Mostly NPs inhibit the growth of various pathogenic and non-pathogenic bacteria with proportionally similar pattern with minor degree of variations from cell integrity loss to cytotoxicity to DNA damage [199]. Against *Staphylococcus aureus*, silver NPs cause cytotoxic damage through formation of the reactive oxygen species which ultimately bind with multiple organelles of the cell due to their unstable nature [200–203].

Moreover, these nanoparticles kill the bacterial pathogens through nucleic acid denaturation and even the damage to the different enzymes which are necessary for their multiple metabolic activities. Furthermore, AgNPs nanocomposites impart irreversible damage to the cells and DNA, ultimately

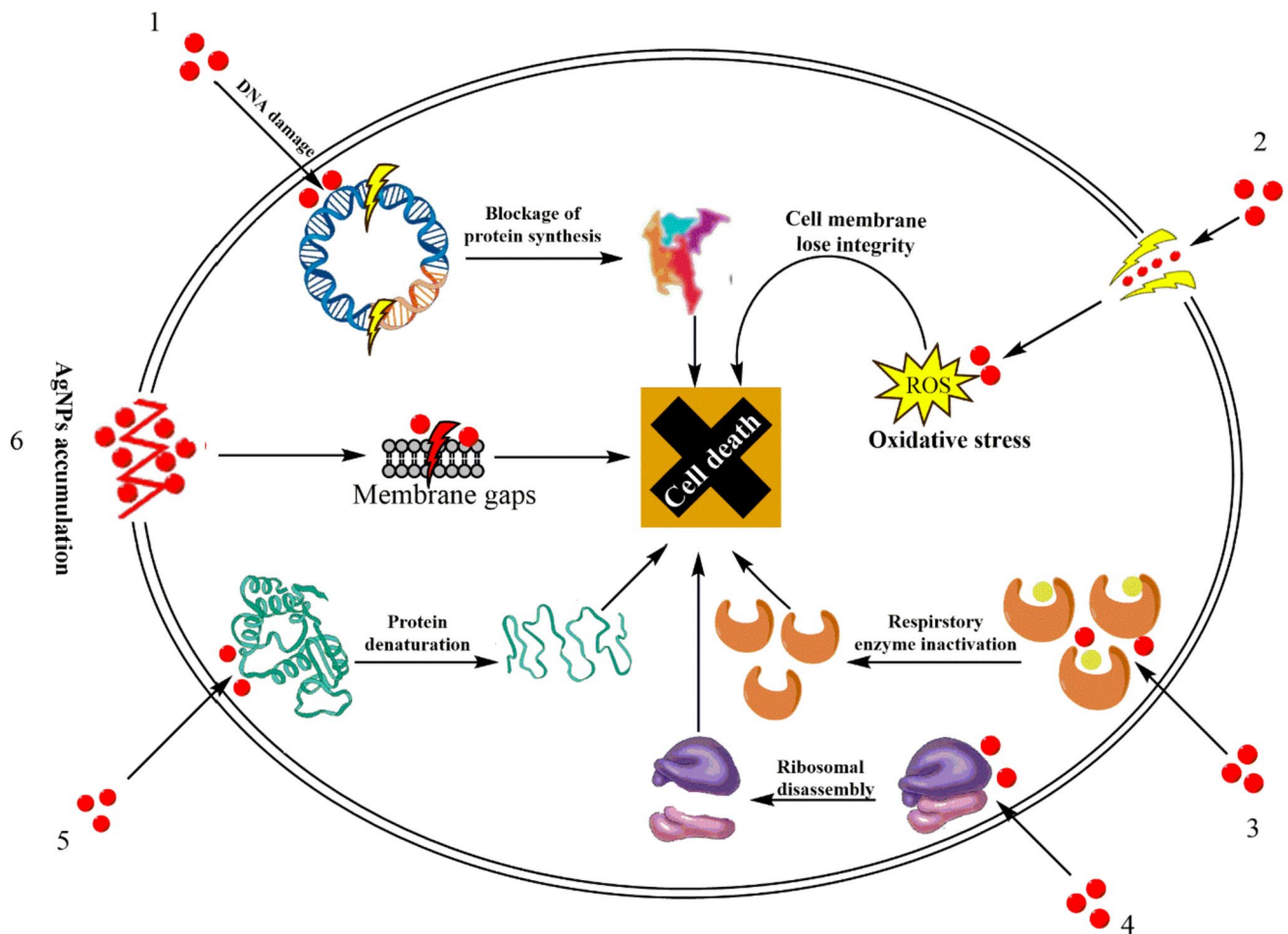


Fig. 6 Modes of action of antimicrobial activity of Silver Nanoparticles (AgNPs)

causes the mortality [204–207]. Wang et al. [208] and Nishu et al. [209] reported that AgNPs inhibit the respiration-related activities of susceptible microorganisms. Overall, different biogenic and metallic NPs have shown various degrees of antibacterial potential against Gram-positive and Gram-negative bacteria. In this regard, AgNPs are proven to be more efficacious against Gram-positive due to their comparatively thin layer of peptidoglycan.

ZnONPs cause severe damage to other Gram-positive rod bacteria including *Bacillus*, *Mycobacterium* and *Streptomyces* causing the charge-dependent toxicity which subsequently destabilizes the membrane potential of the pathogens, thus causes death [210].

Damage to the genetic material (DNA) through inhibition of the replication phenomenon, deterioration of the cytoplasmic membrane or even ATP level modifications through intercalation of the nitrogenous bases are the most common pathways of the copper-based NPs against *Staphylococcus* species [211]. Certain copper-chitosan conjugated NPs also impart large surface cell wall collapse, cell leakage and wrinkled cell wall which ultimately inhibit the growth of

Mycobacterium tuberculosis [212]. Cell cycle arrest against the *Mycobacterium* followed by cell disintegration through pore formation using selenium NPs is also reported by Estevez et al. [213].

Moreover, different researchers reported the morphological damage, and cytotoxicity by NPs accumulation in the *Enterococcus* species as a possible mode of bactericidal activity against different *Enterococcus* species including *Enterococcus faecalis* [214]. Iron oxide and other NPs also have the ability to counter the various Gram-positive bacteria including *Bacillus sp.* and *Enterococcus sp.* by inhibiting the biofilm formation individually as well as in a synergistic manner with various novel synthetic drugs [80–84, 215, 216].

4.1.2.2 Nanoparticle's Mode of Action Against Gram-Negative Bacteria AgNPs Block DNA replication and mutilation of the cytoplasmic membrane and abrupt intracellular changes of ATP which lead to bactericidal activity in *Salmonella typhi* [189, 217]. Biosynthesized NPs from various juice extracts from medicinal plants like *Citrus macroptera*

harbor significant bactericidal potential through inhibition of the biofilm formation against Gram-negative bacteria including *Pseudomonas aeruginosa* [80–83].

The bactericidal potential is expressed by NPs as they modulate the permeability of cell membranes and mutate the process of respiration [189, 218, 219]. Morones et al. [189], Mahapatra et al. [220] and Saberpour et al. [221] revealed that nanosilver alters the membrane structure against *Vibrio cholera*. Cell membrane alteration in *Klebsiella pneumonia* is the leading cause of mortality after exposure to silver-based NPs reported by Manjumeena et al. [222], Tamayo et al. [181], Siddique et al. [223] and Pareek et al. [224]. Lysakowska et al. [225], Salih et al. [226], and Singaravelu et al. [227] depicted in their study that cytoplasmic changes induced by silver nanoparticles are responsible for bactericidal activity against *Acinetobacter baumannii*.

4.1.3 Molecular Basis of Nanoparticles Mediated ROS Generation

ROS production is a significant byproduct of NP-mediated damage [228]. ROS elements include free radicals such as singlet oxygen ($^1\text{O}_2$), hydroxyl (HO^\bullet), superoxide ($\text{O}_2^{\bullet-}$) and non-free radicals like hydrogen peroxide (H_2O_2), nitric oxide (NO), hypochlorite (OCl^-) and hypochlorous acid (HOCl) [229]. They are produced primarily in organelles like the peroxisomes, endoplasmic reticulum (ER), microsomes, cell membrane complexes and, most importantly, mitochondria [230]. Oxygen is utilized for the production of water during oxidative phosphorylation by transfer of electrons via electron transport chain in mitochondria (ETC). Some of these electrons are taken up by molecular oxygen to produce $\text{O}_2^{\bullet-}$, which can be converted into OH^\bullet and other forms of ROS [231].

The mechanism behind NPs mediated ROS production differs amongst NPs. The majority of nanoparticles derived from metals can cause free-radical-mediated toxicity via Fenton-type reactions [232]. Metal ions produced by nanoparticles have been proven to interact with chemocatalysis and redox cycling through the Fenton reaction [$\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{HO}^\bullet + \text{Fe}^{3+} + \bullet\text{OH}$] or Fenton-like reaction [$\text{H}^+ + \text{Ag}^+ \text{H}_2\text{O}_2 = \text{Ag}^+ + \text{H}_2\text{O} + \bullet\text{OH}$] as shown in Fig. 7 [233]. The isolated metal ion(s) (Ag^+) also deactivates cellular enzymes, disrupts membrane structure, disrupts the electron-shuttling process, reduces redox potential levels, lowers mitochondrial membrane potentials (MMP) and increases intracellular ROS accumulation [234]. NPs have also been shown to increase intracellular ROS levels by interfering with the electron transfer process raising the $\text{NADP}^+/\text{NADPH}$ ratio, and interfering with mitochondrial activity [235]. NPs also disrupt the expression of oxidative stress-related genes such as

ahpC soxR, soxS, and oxyR, antioxidant genes such as gpx 1 and sod1, and gene-producing NADPH met9. The instabilities in the transcription of oxidative and antioxidant genes triggered by NPs hasten the formation of intracellular ROS [236].

4.1.3.1 Mechanism of ROS Generation NPs must interact with cell membranes to infiltrate the cell. Nanomaterials are transported into cells through encapsulation in vesicles via endocytosis [237]. Internalization of NPs may or may not depend upon caveolin or clathrin proteins [238]. Metabolic processes that contribute to the formation of intracellular ROS by NPs include binding with mitochondrial components, growth factors activation, and activation of membrane complexes [239].

Mitochondria is a primary organelle in the NPs mediated production of ROS. NPs induce depolarization of the mitochondrial membrane and disrupt electron transport chain by activating NADPH-related enzymes [240]. Hence, After NP exposure, an electron-transport chain is inhibited, raising intracellular concentrations of $\text{O}_2^{\bullet-}$ through transferring electrons from respiratory complex carriers to O_2 [241]. Human fibroblasts and glioblastomas exposed to NPs were shown to accumulate more AgNPs, CuNPs, ZnONPs, etc., in mitochondria which disrupted electron-transport chain and, as a result, high levels of ROS production [242]. In the majority of bacteria, metal ions interacted with NADH dehydrogenase, preventing electron transport to O_2 and the production of large amounts of ROS [243].

Moreover, the conversion of GSH into glutathione disulfide, caused by NPs-induced free radical generation, contributes to oxidative stress [244]. The activation of ROS-associated receptors and enzymes by NPs also contributes to the production of intracellular ROS [245]. The ability of NPs to induce DNA damage is due to the formation of the free radical HO^\bullet , which binds with DNA and give rise to 8-hydroxyl-2'-deoxyguanosine (8-OHdG), which eventually causes DNA damage [246].

1. NPs are internalized into cells via endocytosis.
2. It leads to production of endocytotic vesicles.
3. Then particle ions are released from endocytotic vesicles into a cell.
4. The primary causes of ROS formation by NPs. Contact with mitochondrial membrane.
5. Attachment to NADPH oxidase which causes loss of electron by oxidizing NADPH and transfer electron to oxygen, converting it into superoxide radical.
6. The majority of nanoparticles cause free-radical-mediated toxicity via Fenton-type reactions. The aforementioned factors cause ROS production and associated effects, which include cell cycle arrest, DNA damage, modification in apoptosis, and cell membrane damage which ultimately leads to cell death.

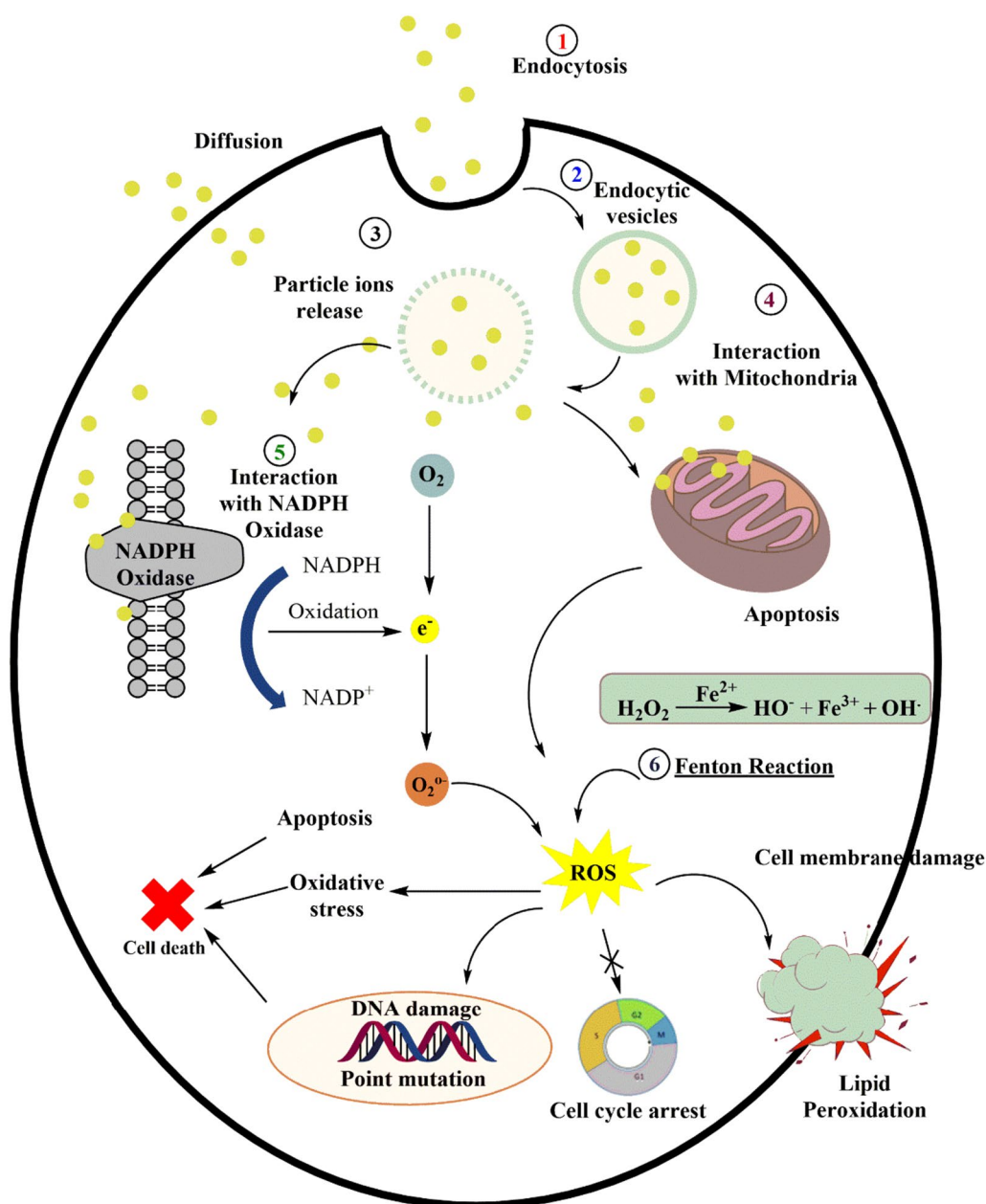


Fig. 7 Schematic illustration of the pathways involved in ROS generation by Nanoparticles (AgNPs, ZnONPs, CuNPs, TiO₂, CoNPs)

4.2 Antimicrobial Potential of ZnO NPs

ZnO NPs are fetching considerable attention due to their unique properties like low toxicity, high absorption rate, and biological activities including antibacterial and antioxidant potential [247–252]. Several studies have reported the antibacterial properties of ZnO NPs and their non-toxicity to human cells [253–255]. Zinc oxide nanoparticles are being used in food packaging as an antimicrobial agent against *Salmonella*, *Staphylococcus aureus*, *C. jejuni*, and

E. coli as these are major foodborne bacteria to cause food deterioration [256–258].

They show a wide range of antibacterial activities against Gram-positive and Gram-negative bacteria. Moreover, Gram-positive bacteria are found to be more susceptible to ZnO NPs as compared to NPs of other elements of the same group [234, 250, 251]. The antibacterial activity of ZnO NPs is dose and size-dependent, an increase in NPs concentration results in the increased efflux of cytoplasmic content while it decreases with the increase in the size of nanoparticles as

revealed by several studies conducted by Tiwari et al. [259], Espitia et al. [260], Abebe et al. [261], and Fahimminisha et al. [262].

4.2.1 Mode of Action of ZnO NPs Against Different Bacterial Strains

Although the mechanism of toxicity of ZnO is still controversial and requires deep explanation, the proposed mode of action includes contact between ZnO NPs and bacterial cell wall followed by loss of integrity and disruption of the cell wall, hence release of intracellular contents and generation of reactive oxygen species (ROS) [252, 262–266]. Moreover, various studies suggest the dissolution of ZnO NPs into Zn^{2+} which binds to major biomolecules like proteins and carbohydrates results in the cessation of vital functions of bacteria [234, 267]. Antimicrobial properties of ZnO NPs can also be attributed to the photo-induction process since being a semiconductor ZnO has high photocatalytic efficiency. This photoconductivity is increased when exposed to UV light as it stimulates the interaction between ZnO and bacterial cells [255, 268]. Although Adams et al. [269], Hirota et al. [270], Lakshmi Prasanna & Vijayaraghavan [271], and Jeong et al. [272] provided evidence of ROS generation even under dark conditions [273]. ZnO NPs increase cytotoxicity predominantly by ROS production, which causes oxidative damage and the release of inflammatory chemicals, eventually leading to cell death as depicted in Fig. 7 [274].

The generation of ROS is the most commonly reported mechanism for antibacterial activity which occurs as a result of the formation of different intermediates, the generation of hole pairs and their reaction with oxygen or water as

reported by Abebe et al. [261]. Both, direct (inside the bacterial cell) and indirect (outside the bacterial cell) generation of ROS has been observed by Thakur et al. [275]. ROS causes damage to the bacterial cell's biomolecules including proteins and DNA [276] (Fig. 8).

4.2.2 Specific Bacterial Strains and ZnO NPs Mode of Action

4.2.2.1 *Campylobacter jejuni* Tiwari et al. [258] reported the formation of cell wall blebs and irregular surfaces in *C. jejuni* when exposed to ZnO NPs. The disruption in the cell membrane of *C. jejuni* and overexpression of the genes (*ahp C* and *KatA*) that are triggered by oxidative stress was observed by Xie et al. [277]. Altered gene regulation in response to ZnO NPs was also confirmed by Campbell et al. [278] and Cerasi et al. [279]. The formation of ZnO^{2+} ions from immobilized ZnO NPs also curbed the growth of *C. jejuni* in raw chicken meat [280].

4.2.2.2 *Staphylococcus aureus* The growth of *Staphylococcus aureus* was inhibited by a complex mechanism involving different metabolic pathways including disruption of sugar metabolism and amino acid biosynthesis instead of ROS generation as described by Kadiyala et al. [281]. Lallo da Silva et al. [282] observed the accumulation and internalization of nanoparticles within the bacterial cell when exposed to ZnONPs.

Another novel mechanism was proposed by Kadiyala (2018) which suggested the killing of *Staphylococcus aureus* by enhanced expression of pyrimidine biosynthesis and upregulation of carbohydrate degradation rather than ROS generation. However, Navarro-López et al. [283] described

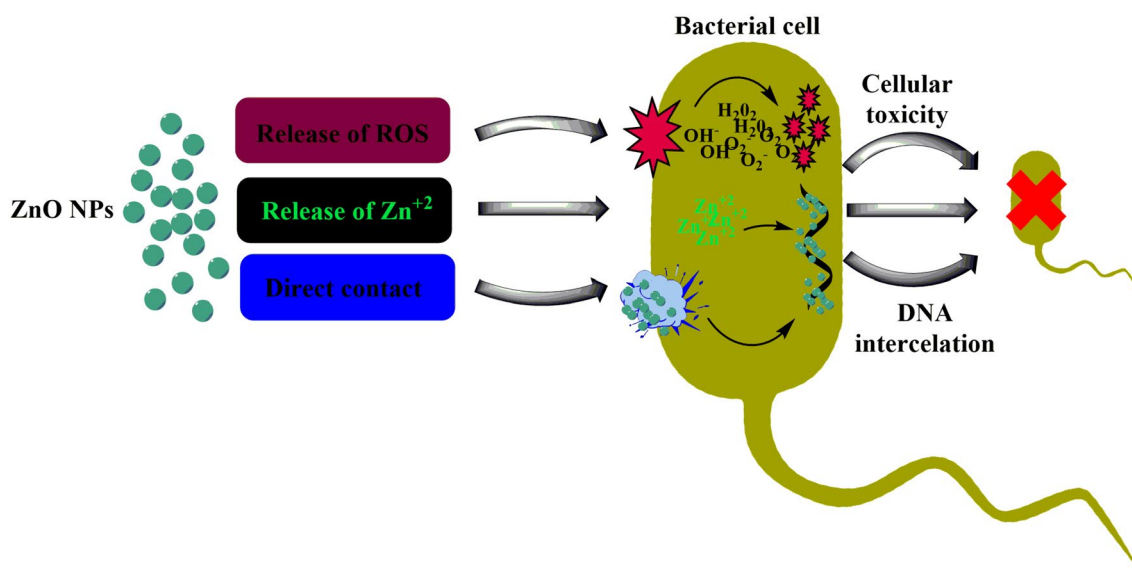


Fig. 8 Mode of action of Zinc oxide nanoparticles (ZnO NPs)

the ROS generation as the possible mechanism against *Staphylococcus aureus*.

4.2.2.3 *E. coli* Li et al. [284], Pasquet et al. [285], and Navarro-López et al. [283] reported that cell wall damage, increased membrane permeability, ROS production and release of Zn^{2+} ions following the dissolution of ZnO NPs led to the toxicity in *E. coli* when exposed to the ZnO nanoparticles. It was also observed that Zn^{2+} ions had a smaller effect when compared to the toxicity caused by ROS [286].

4.2.2.4 *Staphylococcus epidermidis* Akbar et al. [287] described the morphological and physiological changes in the bacterial cell along with pitted and deformed cell walls in *Staphylococcus epidermidis* when treated with ZnO NPs. Palanikumar et al. [288] reported the ROS generation and their subsequent accumulation in the cytoplasm as a possible mechanism against *Staphylococcus epidermidis*.

4.3 Antimicrobial Potential of Copper Nanoparticles (CuNPs)

Copper (Cu) is naturally present in certain food groups in small concentrations and acts as a catalyst for some enzymes. However, when found in high concentration, it was reported to have antimicrobial properties against some major food-borne bacteria including *Campylobacter jejunii* and *Salmonella enterica* [289–292]. Copper has also been recognized as an antimicrobial material by US Environmental Protection Agency (EPA) [293]. The antimicrobial property of copper has led the researchers to synthesize its nanoparticles to enhance its antimicrobial effectiveness associated with high surface area to volume ratio of the NPs. Moreover, the use of CuNPs in many biomedical applications can be cost-effective due to their low cost and ubiquitous availability [294–296].

CuNPs have been stated to exhibit broad-spectrum antimicrobial activity [295, 297, 298]. Many researchers have confirmed the antimicrobial properties of CuNPs against a number of Gram-positive and Gram-negative bacteria [299–302]. They are even reported to have superior antimicrobial properties than AgNPs against *B. subtilis* and *E. coli* and can be used as substitutes for expensive AgNPs [300, 303].

However, the formation of oxides by CuNPs on exposure to atmospheric layer can limit the antimicrobial properties [304]. To prevent oxidation during synthesis and storage of CuNPs, an inert atmosphere is required which increases the complexity of the process. Nonetheless, the oxidation of the CuNPs can be avoided by using green synthesis methods [305, 306].

Biomolecules in the plant materials including flavonoids, phenols, and tannin provide stability by capping and prevent

oxidation of NPs [307, 308]. Moreover, the use of green synthesis for NPs production is convenient, eco-friendly, and inexpensive [234]. In this regard, Pérez-Alvarez et al. [306] reported the synthesis of CuNPs using cotton. The subsequent NPs formed were found to be stable to oxidation and could be stored for months without any change in the properties.

4.3.1 Mode of Action of Cu Nanoparticles Against Different Bacterial Strains

The information regarding mode of action of CuNPs against microbes is quite limited but proposed mechanisms suggest that the CuNPs release Cu^{2+} in interaction with cell wall. These ions get adsorbed on the cell wall of bacteria which later leads to formation of pits in the membrane and loss of cell membrane integrity [295, 309–312]. The affinity of CuNPs towards amines, carboxyl group and sulfhydryl groups in the peptidoglycan layer denatures the proteins of cell membrane [313–315]. CuNPs can also penetrate via endocytosis in plasma membrane. Once inside the cell, Cu^{2+} binds to DNA molecule and disrupt the helical strands by cross-linking, leading to disorganization of nucleic acid molecules [227, 237, 316–318].

Metal oxide NPs such as Cr_2O_3 , Co_3O_4 , Mn_2O_3 , Ni_2O_3 , CuNPs, and CoO cause cytochrome c oxidation and oxidation of NADPH into $NADP^+$ leading to oxidative stress [319]. Some photon-activated NPs, for example, TiO_2 NPs produce electrons with sufficient amount of energy to convert O_2 into 1O_2 (singlet oxygen), which causes cellular damage by binding cellular proteins, nucleic acids and lipids as shown in Fig. 7 [320].

The cell may be subjected to oxidative stress due to generation of reactive oxygen species (ROS) as reported by Applerot et al. [321] and Chatterjee et al. [316] as shown in Fig. 9. The increased ROS production disrupts several metabolic pathways through enzyme inactivity and protein dysfunction [322, 323]. The antimicrobial activity of CuNPs is greatly dependent on particle size, composition of bacterial cell wall, and nature of nanoparticles.

4.3.2 Specific Bacterial Strains and CuNPs Mode of Action

4.3.2.1 *E. coli* Chatterjee et al. [316] concluded that the mechanism of toxicity of CuNPs against *E. coli* was found to be the release of Cu^{2+} , followed by loss of integrity of plasma membrane. However, generation of ROS was not reported. While other studies investigated the interaction of CuNPs with cell wall and reported the generation of ROS inside different *E. coli* strains [303, 311, 324]. Metryka et al. [325] and Sharma et al. [326] stated that the loss of cell membrane integrity, ROS generation and leakage of intracellular content is the cause of bacterial cell death.

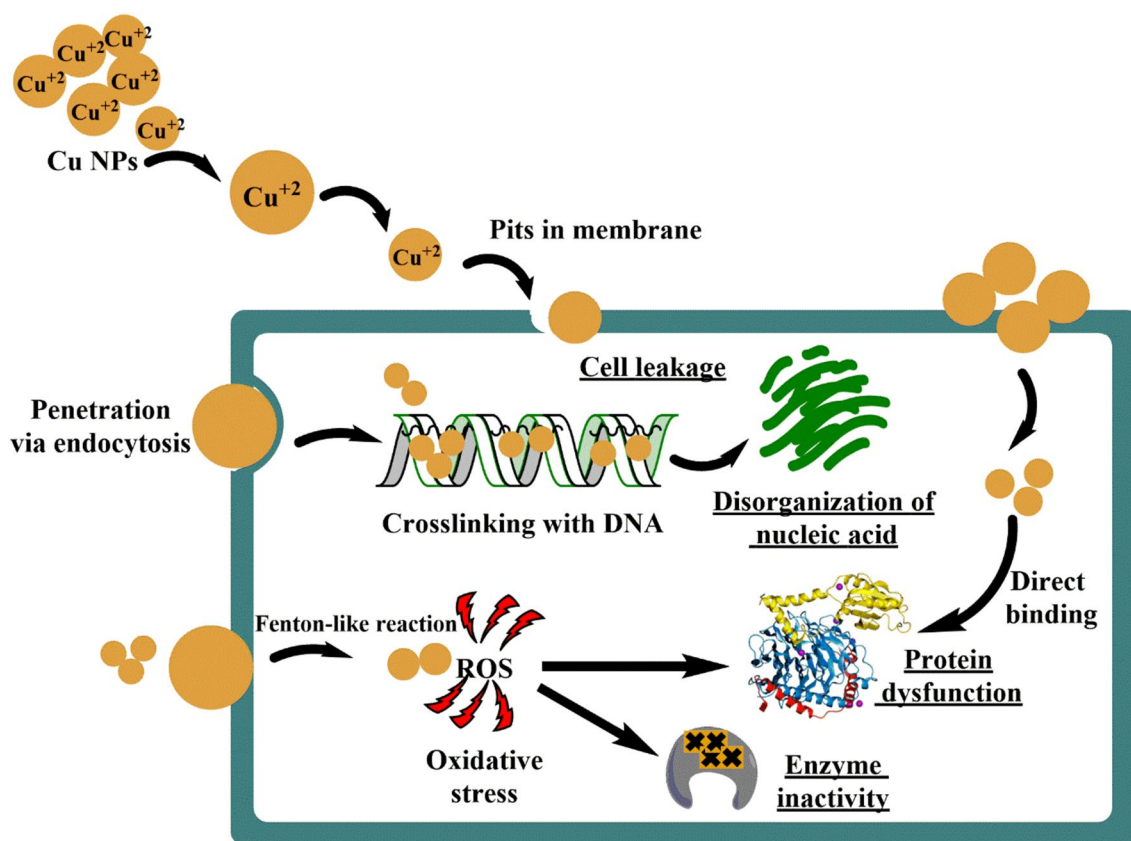


Fig. 9 Mode of action of copper nanoparticles (CuNPs)

4.3.2.2 *B. subtilis* The interaction of Cu²⁺ ions and their subsequent binding with the amines and carboxyl groups in the peptidoglycan layer was observed by Ren et al. [315] against *B. subtilis*. Li et al. [327] reported that damage to outer membrane and protein disruption are responsible for cellular toxicity. Phan et al. [328] suggested that damage to bacteria was dependent on copper ions (Cu²⁺) concentration and size/shape of the nano copper.

4.3.2.3 *Staphylococcus aureus* Li et al. [329] and Yadav et al. [330] reported the damaged and wrinkled cell wall, increased permeability of plasma membrane, and leakage of intracellular material in *Staphylococcus aureus* when exposed to Catechin-Cu nanoparticles.

4.4 Antibacterial Properties of Titanium Dioxide (TiO₂) Nanoparticles

Titanium dioxide nanoparticles have been explored widely due to their high stability and nontoxic nature. Besides having unique optical properties, TiO₂ is an excellent photocatalyst which makes it ideal in antimicrobial applications [331–335]. The antibacterial activity has been

explored against a diverse range of Gram-positive and Gram-negative bacteria [336, 337]. Albukhaty et al. [338] prepared TiO₂ NPs using sol–gel technique and evaluated their antibacterial potential against *S. aureus* and *E. coli*.

Modifications of TiO₂ NPs by *Garcinia zeylanica* and grape seed extract led to enhanced antibacterial activity against *S. aureus*, Gram-negative (*P. aeruginosa*) and Gram-positive (*S. saprophyticus*) respectively [339, 340]. Azizi-Lalabadi [341] further modified the TiO₂ NPs by embedding them into 4A zeolite and depicted their increased bactericidal potential against *P. fluorescens* and *E. coli*. The antibacterial activity of TiO₂ NPs was found to be size and zeta potential dependent i.e., NPs with smaller diameter and more positive zeta potential exhibited higher bactericidal activity [342]. An in vivo investigation found that exposure to Ti, Ag, Cu, and Fe NPs causes genotoxicity by nucleic acid damage. Resulting oxidative stress stimulates signaling pathways leading to the activation of inflammatory mediators, including interleukins and tumor necrosis factor [343]. Figure 7 shows the molecular basis of ROS production which is also associated with the inflammatory reactions induced by metallic nanoparticles (SiO₂ NPs & TiO₂ NP).

4.4.1 Mode of Action of TiO₂ NPs Against Different Bacterial Strains

Although, TiO₂ NPs possess catalytic properties, TiO₂ NPs have shown antibacterial activity with and without UV illumination which hints the presence of toxicity mechanisms aside from photolytic reactive oxygen species (ROS) generation [344–347]. The mechanism of UV-illuminated TiO₂ NPs includes production of ROS including superoxide ions (O^{•−}) and hydroxyl radicals (OH[•]) by reduction of oxygen and oxidation of H₂O as illustrated in Fig. 7. This mechanism was found to be in consistent with other photolytic reactions [344, 348, 349].

Generated ROS disrupt the ionic balance, oxidize the cell membrane components and lead to destruction of plasma membrane. After entering the cytosol, TiO₂ NPs alter the gene expression by discontinuing the enzyme activity and changing the structure of macromolecules in the bacterial cell [350–352]. Sohm et al. [353] investigated the bactericidal action mechanism of TiO₂ NPs in a dark environment by exposing *E. coli* to them. It was illustrated that NPs adsorbed on the cell surface and induced depolarization and instability of plasma membrane. Loss of membrane integrity contributed to leakage of K⁺ and Mg²⁺ ions, entrance of Na⁺ to the cell, and respiratory chain deficiency due to

exhaustion of intracellular ATP level. A similar mechanism was proposed by Seil and Webster [335] and Nemattalab et al. [354]. Sohm et al. [353] and Pagnout et al. [355] also concluded that ROS generation had a trivial effect in causing toxicity in dark conditions.

4.4.2 Mode of Action of TiO₂ NPs Against Specific Bacterial Strains

4.4.2.1 *E. coli* Khan et al. [356], Albukhaty et al. [338] & Nemattalab et al. [354] observed that TiO₂ NPs caused ROS generation and phospholipid peroxidation that led to the death of *E. coli*. Different researcher also documented that TiO₂ NPs may also attach to the outer wall of the bacteria and make small pores (porins), which disturb the cell integrity and leads to the death of the bacteria. These NPs have also the ability to deteriorate the activity of various vital enzymes necessary for important functions like pathogenicity [297, 298, 357]

4.4.2.2 *Staphylococcus aureus* Abdulrahman et al. [358], Bekele et al. [359], Albukhaty et al. [360] evaluated the bactericidal activity of TiO₂ NPs and stated that destruction of the outer membrane and leakage of the cell content was a major cause of bacterial cell death (Fig. 10). Some

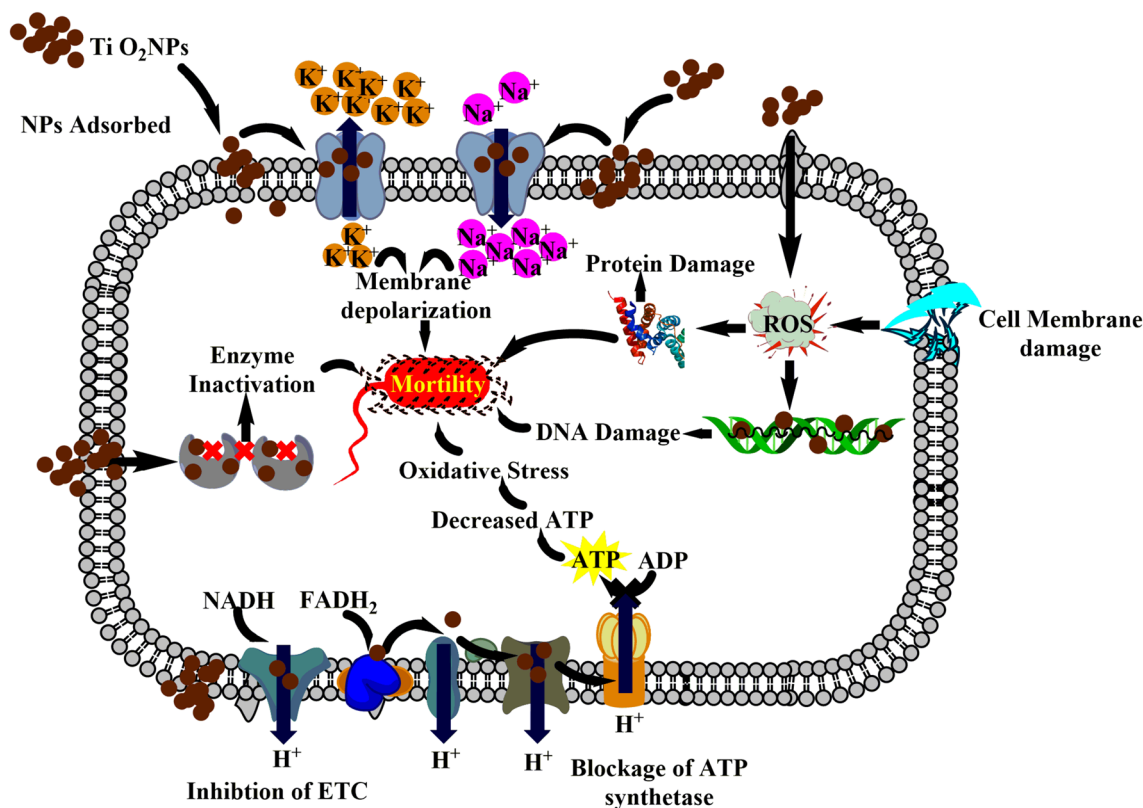


Fig. 10 Mode of action of TiO₂ nanoparticles

other researchers also reported that the titanium-based NPs could also generate the non-stabilized reactive oxygen species (ROS) which bind with multiple macromolecules of the bacteria including the nucleic acids, proteins, and lipids thus damaging the DNA machinery and causing cell death [201, 297, 298].

4.4.2.3 Streptococcus Loss of cell viability and outflow of K⁺ ions were observed in the cells of *Streptococcus sobrinus* which was followed by slow leakage of intracellular material when exposed to TiO₂ NPs [361]. Moreover, Besinis et al. [362] and Pourhajbagher et al. [363] documented that these NPs with size less than 100 nm have the potential to damage the outer morphology of the bacterial body as well as the damage to the DNA. Miron et al. [364] reported the membrane damage in *Streptococcus pneumoniae* using atomic force microscopy. Khan et al. [365] documented the internalization of the nanoparticles followed by ROS generation and DNA damage.

5 *Pseudomonas aeruginosa*

Amezaga-Madrid et al. [366] and de Dicastillo et al. [331] documented the impairment of the cell wall and structural damage of the plasma membrane that resulted in subsequent leakage of cellular material of *Pseudomonas aeruginosa* as shown by SEM and TEM. Rajkumar et al. (2019) reported the antibiofilm activity of the titanium-conjugated NPs which stops the intercellular bacterial communications within colonies and makes them susceptible for cytotoxic damage through direct contact of the NPs. Furthermore, such NPs can also cause mortality through ROS production [367].

5.1 Antimicrobial Potential of Cobalt Nanoparticles (Co NPs)

The transition metal, Cobalt has become of special interest because of the unique physicochemical properties manifested in Co NPs due to the quantum size effects [368]. The nano-sized cobalt particles are known to have catalytic, optical, biomedical and antibacterial properties [369, 370]. They are being explored as an active therapeutic agent against infectious diseases [371]. Synthesis of Co NPs is inexpensive, biocompatible, and does not require any additional stabilizing agent [372]. They are non-toxic to body at lower concentrations but highly effective against bacteria and fungi even at minimal levels of concentration making them favorable for biological applications [373].

The antibiotic potential of Co NPs was found to be stronger as compared to standard antibiotic drug ciprofloxacin [374]. The green method synthesized Co NPs have

shown promising antibacterial activity against different bacterial strains including *E. coli*, *S. aureus*, and *Klebsiella pneumonia* [375].

5.1.1 Mode of Action of Co NPs Against Different Bacterial Strains

Igwe and Ekebo [370] reported the possible antibacterial mechanism of cobalt nanoparticles bio-fabricated from the leaf extract of *C. odorata* against *E. coli*, *K. pneumonia*, *S. aureus*, and *S. pyogene*. The study suggested the direct contact of Co NPs owing to their small size (20–49 nm) with the outer surface of pathogens led to its rupture and eventually cell death. Metal ions bearing a positive charge are strongly attracted to cell membrane carrying the negative charge that initiates the loss of cell membrane integrity and penetration of ions inside the cell [376]. Kharade et al. [377] also suggested a similar mechanism of CoNPs against *Bacillus subtilis* and *Escherichia coli*.

Another mechanism against bacteria was documented by Shriniwas and Subhash [378] involving the destruction of protein synthesis (Fig. 11). Similarly, Guan et al. [379] reported the physiological changes in bacterial cells by disrupting transcriptional regulation caused by Co NPs. Abdal Dayem et al. [235] reported that Co NPs influence oxidative stress through reactions between oxidized metal ions and H₂O₂ to produce free radicals. This further contributes to DNA damage and protein dysfunction. The interaction of cobalt ions with bacterial enzyme thiol and subsequent imbalance of electron transport chain is another major factor causing bacterial cell death. [380, 381].

5.1.2 Mode of Action of Co NPs Against Specific Bacterial Strains

5.1.2.1 *E. coli* Satpathy & Manikandan [382] demonstrated the bactericidal mechanism of *E. coli* which is caused by binding of Co NPs with cell wall due to increased lipophilicity of metal ions.

5.1.2.2 *Staphylococcus aureus* Co NPs showed antibacterial activity against this multi-drug resistant bacteria through electrostatic interaction of Nps with its cell wall [383]. Another possible mechanism could be the release of cobalt ions disrupting the DNA replication machinery and protein inactivation [384].

5.1.2.3 *Pseudomonas aeruginosa* Co-NPs exhibited adhesion to the cell wall and altered its permeability. After penetration, ROS production and change in cell signaling caused cell death [385].

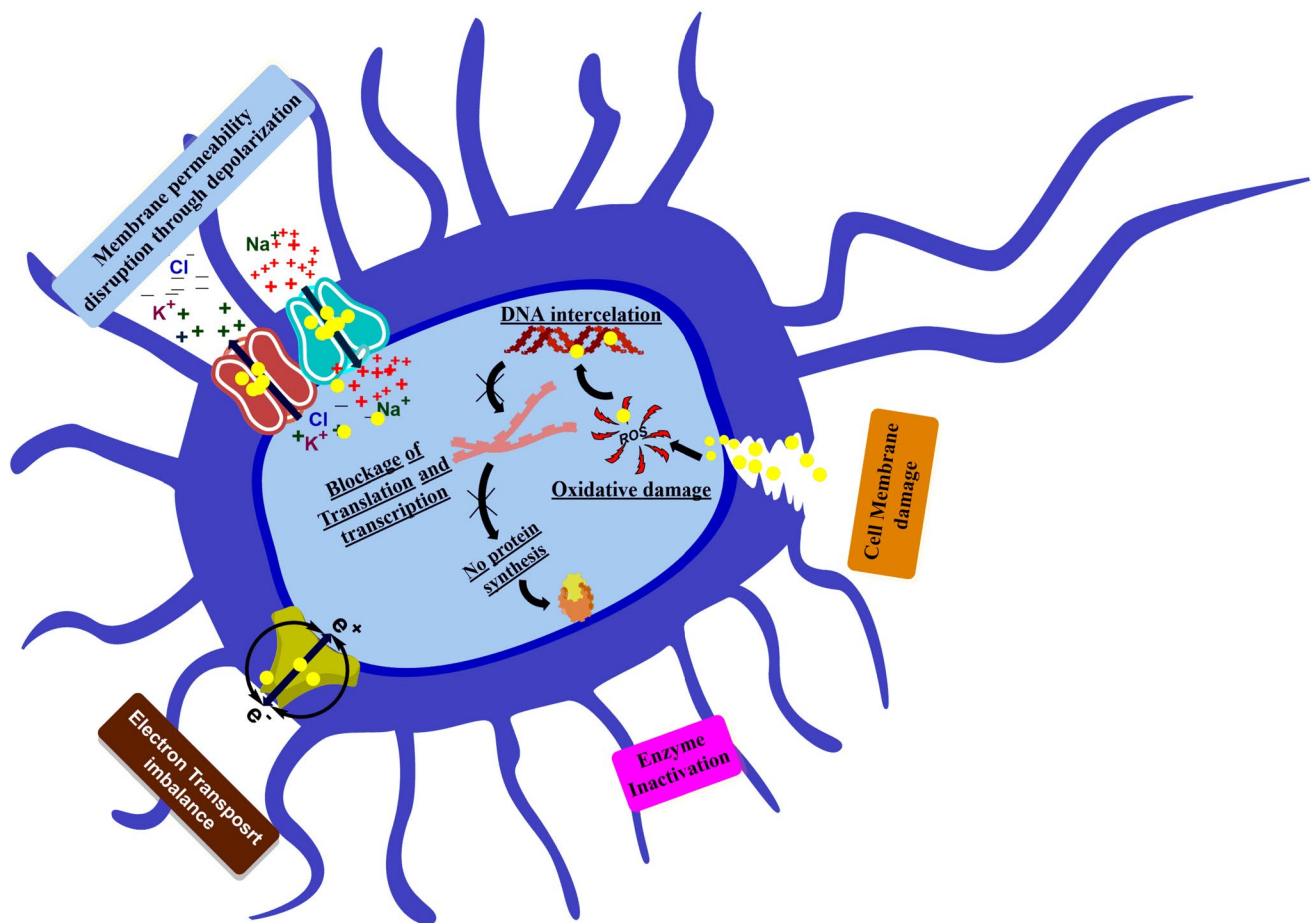


Fig. 11 Mode of action of Cobalt Nanoparticles (Co NPs)

5.1.2.4 *Bacillus Subtilis* Sivachidambaram et al. [386] suggested that generation of ROS was the key factor in causing bacterial cell death.

6 Discussion

Synthetic drugs/antibiotics have revolutionized the frontline medications for treatment of various life-threatening ailments across the globe but their unregular use has become a nightmare in the form of antimicrobial resistance (AMR) or development of multiple drug resistant (MDR) pathogenic strains [21, 387]. Surprisingly, antimicrobial resistance has paced out the discovery of novel antibiotics to counter the resistance phenomenon. Epidemiological statistics of 204 countries and their peripheries estimated that 4.95 million people with infections due to MDR pathogens in 2019 and more than 1.2 million mortalities due to AMR [388]. Moreover, due to current wave of SARS-CoV-2, worse conditions regarding drugs resistance being anticipated due to administration of a bulk of antibiotics to patients with viral

infections [389–391]. With the passage of time, majority of the bacteria have developed various intrinsic and adaptive/acquired modes to escape from the influence of these conventional therapeutics [50, 53].

During intrinsic antibiotic resistance modes, bacteria get rid of the antibiotics by up-regulation of efflux pumps, activation of drug-altering enzymes and altering the target sites of the antibiotics as depicted in Figs. 6 and 12 [43]. On the other side, in acquired resistance phenomenon, susceptible bacterium develop resistance by altering the genetic makeup. Pathogens may also become resistant through chromosomal mutation, genetic rearrangements or adopting the exogenous genetic material through transformation, transduction and conjugation as shown in Fig. 2 [46, 47]. Although certain new antibiotics are being approved by FDA but there is no guarantee regarding their efficacy [27]. Moreover, these drugs are not cost-efficient and pose serious threats to healthy tissues.

The current dilemma of antibiotic use has urged the whole scientific community to search for some alternative therapeutic solutions with novel modes of action to overcome the

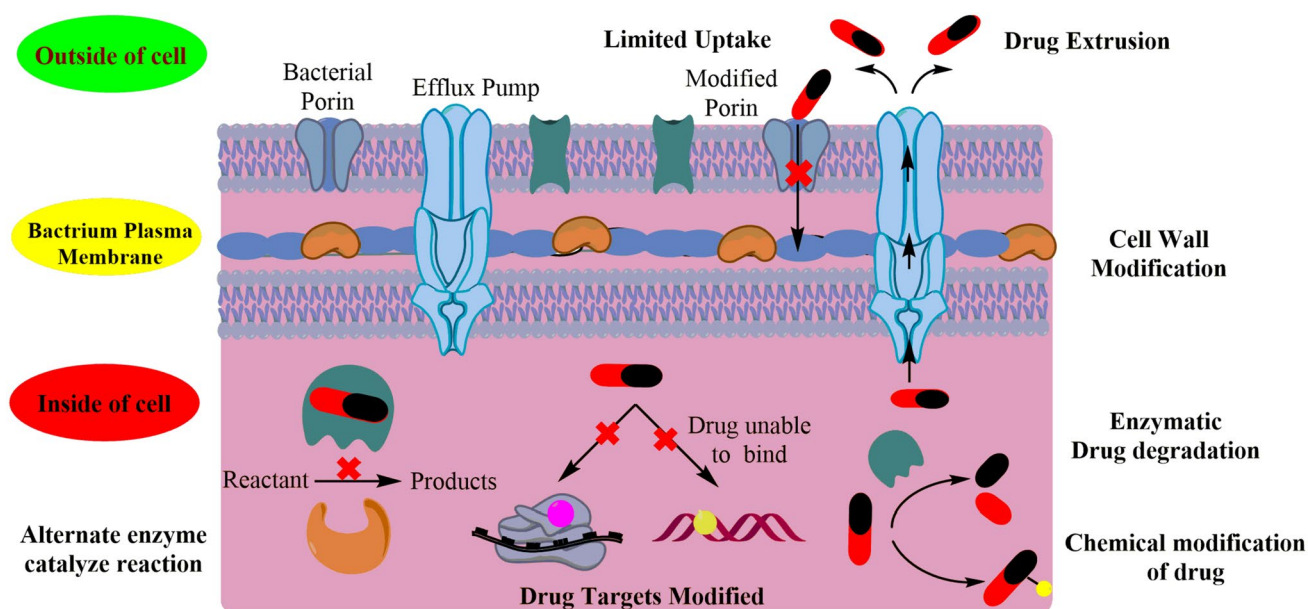


Fig. 12 General modes of AMR and MDR

AMR [36, 392]. In this regard, nanotechnology has emerged as the sole solution to the problem of antibiotic resistance due to its tunable nature and novel physiochemical and biological properties [393, 394]. Nanoparticles employed the application of entity sizes ranging from 1 to 100 nm with large surface-to-volume ratio, and variable interaction ability to the bacterial surface for efficient bactericidal potential [395, 396]. These nanoparticles are being preferred over the conventional clinical approaches as they have some novel mechanism to kill the bacteria or they have ability to modify the already available mechanisms alongside the existing antibiotics in a synergistic manner.

Nanoparticles are usually conjugated with certain reducing agents of chemical origin for required physiochemical bonding or with bio-constituents of living organisms including plants, animal or bacterial origin. Various metals including silver, copper, zinc, cobalt, titanium, gold and silica, etc., are in use for different biomedical applications including antibacterial [396–401]. These NPs in reply of AMR, overcome the problem by adopting the novel pathways including the damage to the outer membranes of the bacteria through pores formation after destabilization of the membranes [402]. As these biogenic nanoparticles are less than 100 nm, they might have the significant ability to cross the cell wall of the bacteria to reach the internal organelles for efficient damage.

Many researchers also reported the high mortality rate of the bacteria after exposure to smallest size NPs as compared to the large-sized NPs of same metal [148, 149, 403]. Mageshwaran et al. [404] also endorsed that NPs with least size have the ability to interact with the genetic material of

the pathogen and thus cause mortality. Furthermore, these NPs inhibit the growth of microbes by many other novel modes including the ROS generation which indirectly cause cellular damage by immediate linkage with the bacterial organelles [110, 252, 405]. Similarly, altering the permeability of the outer membrane of the bacteria through ion channel deterioration is another indirect passage of certain NPs to neutralize the pathogens [385] as shown in Fig. 12. It has now been established by the previous studies that mechanism through which pathogens develop resistance against frontline antibiotics are countered by novel NPs mostly by alternative pathways as clearly shown in Figs. 6, 8, 9, 10 and 11.

7 Toxic Nature of Nanoparticles

Despite showing promising results for various biomedical/clinical applications, nanoparticles have been found to be potentially hazardous [406–410]. To minimize the toxicity caused by NPs, dose optimization is critical. Currently, the concentration of NPs being used in vitro for cell damage is quite high which halts its application to humans. Moreover, translating the results from animal studies to specifically human beings may not be applicable [365, 411].

7.1 Nanotoxicology

Nanotoxicology has fetched the attention of health concerns after the emergence of the use of metallic and biogenic nanomaterials in various biomedical and other health-related

fields. This critical class of novel understanding not only highlighted the potential deteriorative health effects of nanoparticles on humans but also on other animals, plants and even the ecotoxicological role by contributing towards air and water pollution [412]. In this regard, Organization for Economic Cooperation and Development in 2005, raised reservations regarding the health risks associated with the use of nanoparticles for the 1st time. As a result of this awareness, various databases across the globe have been established highlighting the potential benefits and risks of the nanoparticles as well as the standard protocols of acute and chronic toxicity testing [413].

7.2 Types of Toxicity

Dose, duration and frequency of exposure and pathway of administration are the critical factors influencing the toxicity [408, 414, 415]. Nanoparticles can reach into the body through skin (subcutaneous, cutaneous) penetrance, inhalation by lungs, orally (GI tract) and intravenously same as the common routes of other drugs administration. The intravenous route is susceptible to highest toxicity due to direct delivery or mixing of any drug/nanomaterial. In this regard, outcomes or the results of the nanomaterials can be desirable, undesirable or both. Undesirable effects are also then referred as negative or adverse effects like allergic reactions [416, 417]. Regarding the types, toxicity can be immediate or slow based on the time of its symptoms, non-reversible or reversible based on whether the adverse impact is permanent or not and localized or systemic due to its local (on the site of administration) or throughout the body [418]. Elimination time, body metabolism response, absorption and distribution of any nanoparticle could also tune the toxicity. Generally, toxicity after single-dose exposure varies from multiple/repeated exposures.

Therefore, on the basis of exposure, toxicity that is observable during the 1st 24 h of administration is termed as acute while, while the response against any nanomaterial after repeated exposure seen within a month is known as subacute and referred to as chronic if the effect is observable after three months of chronic exposure [417, 418].

The purpose of acute toxicity evaluation is to assess the NOEL (non-observable effect level) and MTD (maximum tolerated dose) of the administered nanomaterials. FDP (fixed dose procedure), LD₅₀ (Dose at which 50% mortality occurs) and ATC (acute toxicity category) are the most common methods to evaluate acute toxicity [419, 420]. Moreover, mechanisms of NPs toxicity as well as organ toxicity are elucidated by the acute and sub-acute toxicity [421].

Immediate behavioral, cardiovascular, hematological and neuronal responses, weight fluctuations as well as clinical manifestations including the effect of NPs exposure to respiration, body movements, dilation or constrictions of

blood vessels, GI tract function, skin and fur and histopathology of vital organs are being monitored during acute and sub-acute toxicity [416, 422]. To assess the long-term safety of the NPs, neurotoxicity, immunotoxicity, ophthalmological parametric study and heart functioning are being considered. Carcinogenesis, reproductive toxicity, embryotoxicity and genotoxicity are necessary to evaluate the sub-chronic and chronic toxic nature of the NPs [422–424].

7.3 Mechanisms of Nanoparticle Toxicity

Physiochemical interactions of the various nanoparticles including silver, titanium, zinc, silica and copper, etc., with any viable cell, are the detriments of their toxic behavior. Variety of toxicity evaluation models like cell lines, zebrafish, rodents, insects (water flea (*Daphnia magna*) and fruit fly (*Drosophila melanogaster*) and many others have been used till now [425–427]. The exact mechanism of acute or chronic toxicity is still ambiguous but their general mechanisms involve DNA, damage, protein dysfunction and others followed by the generation of reactive species [410, 428].

Furthermore, most of the studies have concluded the ROS generation as the major pathway for NPs toxicity using model organisms [417, 429–431]. Yu et al. [432] and Horie & Tabei [433] documented the toxicity of various NPs through generation of ROS in the living cells. In normal physiological state of the body, there is an optimal balance between generation and neutralization of the ROS (singlet oxygen, hypochlorous ions, hydrogen peroxide, superoxide and hydroxyl hydroxyl, etc.) and have a crucial role in cell differentiation, proliferation and death [434, 435]. However, in redox imbalance due to various toxicants, ROS proportion elevates and begins to scavenge the viral macromolecules of the organisms like proteins, carbohydrates, lipids and nucleic acids which ultimately damage the DNA, RNA and various vital enzymes, cytotoxicity and subsequently death [430, 436].

NPs enter the cell through endocytosis and form aggregates. They are considered foreign substances by the body so they may be subjected to phagocytosis by the lysosomes, making their degradation capacity impaired [437]. Further, the toxicity greatly depends on the size, shape, surface area, surface coating and agglomeration. The acute toxicity increases with the decrease in size of NPs [438]. Till now, AgNPs were reported to be most cytotoxic specifically those with the size ≤ 10 nm. They have a tendency to form aggregates in mice organs and induce toxicity, making them a double-edged sword to be used against bacteria [439].

8 Conclusion and Future Perspectives

Metallic biogenic NPs with tunable characteristics like size, shape, and surface area now could produce significant bactericidal potential against a variety of human pathogens. More collaborative work among the scientific community regarding formulation, biosafety, cost-effectiveness, and long-term ecological impact of NPs could lead us to more suitable, economical, and better alternatives to tackle antibiotic resistance with minimum side effects.

Author Contributions MS wrote and edited the manuscript and did the software work. SA edited and evaluated the manuscript. HMT edited and evaluated the manuscript. RA edited the manuscript and help in data acquisition regarding mechanism of NPs action. UF did the graphical and pictorial work. SM did the reference management several times. AH provided the data for manuscript when required. TAM evaluated the data. MAF assisted in software work. HF provided the information regarding antibiotics resistance mechanism.

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Data Availability All data supporting the findings of this study are available within the review article.

Declarations

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