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Synergistic combinations of metal, metal oxide, or metalloid nanoparticles plus antibiotics against resistant and non-resistant bacteria

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ABSTRACT

The emergence of drug resistance in pathogenic bacteria due to the indiscriminate use of antibiotics is a major challenge to global public health. Therefore, improved and more effective antibacterial agents are urgently needed as alternatives to conventional antibiotics. Nanotechnology-based approaches can take advantage of the nano–bacteria interface to improve microbial killing both *in vitro* in and *in vivo*. In this way, modified metal or metal oxide nanoparticles combined with antibiotics could be a novel class of antibacterial agents with synergistic effects against antibiotic-resistant bacteria. This review discusses recent advances in the synthesis and functionalization of these nanomaterials, and considers their advantages and disadvantages.

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Introduction

The fight against antibiotic-resistant bacteria is losing ground owing to the rapid emergence of resistance mechanisms in many bacterial strains [1, 2]. These strains can lead to chronic infected wounds and bacteremia, especially in those patients with some degree of immune suppression [3-5]. Thanks to nanobiotechnology, a wide variety of novel antimicrobial approaches has been developed based on metal or metal oxide nanoparticles (NPs) [6]. These inorganic NPs can inhibit bacteria by damaging the cell wall, bacterial membranes, electron transport chain, nucleic acids, proteins or enzymes by direct binding to biological macromolecules, or by indirect production of reactive oxygen species (ROS) [2, 7, 8]. However, the use of the high doses of NPs needed for antibacterial activity can lead to poor biocompatibility as well as cytotoxicity in physiological conditions [9]. In this regard, the modification of the NP surface with other biocompatible antibacterial agents is an attractive approach [10]. Antibiotics can be used to provide a synergistic effect when combined with metal or metal oxide NPs at safe low doses. For instance, a partial synergistic activity was observed with a combination of Ag/AgCl NPs with vancomycin, erythromycin, or gentamicin against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli* [11]. There are several advantages and

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challenges regarding the functionalization of metal, metal oxide or metalloid NPs with various antibiotics, which we discuss in the following sections.

Cefotaxime

The sustained release of antibiotics is essential issue to achieve sufficient bactericidal effects, particularly against antibiotic-resistant bacteria. One report described the sustained release of cefotaxime with first-order kinetics, by loading this antibiotic onto nanofibers composed of a layered Al-Zn double hydroxide (LDH-cefotaxime with loading of 77.41%) alone, or combined with polyvinyl alcohol/LDH (LDH-PVA-cefotaxime with loading of 67.83%. In contrast to the MBC values, there was a prominent difference in MIC values between cefotaxime antibiotic alone and cefotaxime-Zn/Al LDH against Gram-positive bacteria (*B. subtilis* and *S. aureus*) in comparison with Gram-negative bacteria (*E. coli* and *P. aeruginosa).* Moreover, the percentage of healing in rat skin wounds at day 21 was 96.42%, compared to the positive control of MEBO ointment with 88.09% [12]. Cefotaxime antibiotic can be used as a reducing agent for metal ions such as Au^{3+} to synthesize spherical AuNPs with a size of 21 nm [13]. In a comparative study, five antibiotics including gentamicin, ciprofloxacin, meropenem, ceftazidime, and cefotaxime were combined with Ag-NPs at five concentrations of 0.2, 0.4, 0.8, 1.7, and 3.4 mg/L against carbapenemase-positive *Klebsiella pneumoniae* strains, extended spectrum beta-lactamase (ESBL)-positive *K. pneumoniae*, ESBL-positive *Escherichia coli*, and AmpC-positive *E. coli* strains. For all the strains, a combination of high doses of Ag-NPs plus cefotaxime showed more antibacterial activity with a minimum inhibition concentration (MIC) of 0.03 mg/L compared with lower doses of Ag-NPs plus other antibiotics [14]. As shown in figure 1, conjugation of cefotaxime to chitosan-AgNPs was carried out in three steps, including the green synthesis of AgNPs (7.42–18.3 nm) by *Rosa damascenes* extract, preparation of chitosan-AgNPs (8.05–23.89 nm), and conjugation of cefotaxime to chitosan-AgNPs with a size range of 8.48–25.3 nm. Methicillin-resistant *S. aureus* (MRSA) and multidrug-resistant (MDR) resistant *E. coli* showed an antibacterial effect, with zones of inhibition of 36-37 mm and 23-25 mm diameter, respectively. Additionally, the MIC values of these NPs against the STA5, STA7, and STA8 MRSA strains were 4, 3, and 8 µg/mL, respectively [15].

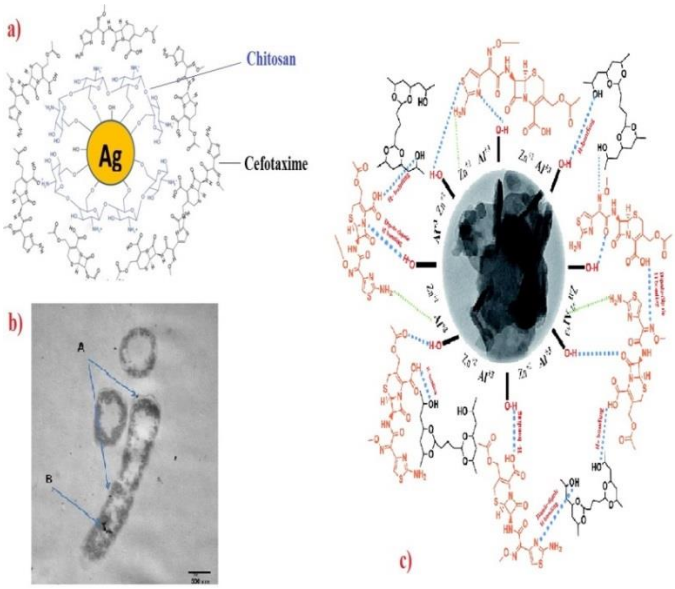

Fig. 1. (a) Schematic illustration of the interaction between cefotaxime, chitosan, and AgNPs to produce the nanoformulation, cefotaxime-chitosan-AgNPs. (b) TEM analysis of *E. coli* under stress caused by cefotaxime-chitosan-AgNPs; the antibacterial effect is attributed to the accumulation of these NPs in the cell wall (A) and inside the cell (B) [15]. (c) Decoration of NPs by a layered Zn-Al double hydroxide plus PVA to allow cefotaxime release, effective antibacterial activity, and improved wound healing [12].

Penicillins

The sustained release of metal ions from metal or metal oxide NPs is the main factor providing a significant antibacterial activity [16, 17]. Therefore, nanocomposites based on Zn-Al-layered double hydroxide with incorporated penicillin G showed sustained antibacterial effects against *E. coli* for up to 10 days, which resulted from release of Zn^{2+} ions [18]. Silicon oxide NPs have several advantages of multifunctionality, low toxicity, large-scale synthesis, appropriate loading capacity, resistance to pH changes, high stability, and hydrophobicity. Silicon oxide NPs can be applied as a surface coating onto other NPs, as a core-shell structure. As one disadvantage, the silanol (Si–O–H) groups at the surface of silicon oxide NPs can result in hemolysis of reticulocytes by interacting with the phospholipids

present in the cell membrane [19]. Silicon oxide NPs can be synthetized by the microemulsion method or the Stober process [20, 21]. Penicillin G-Ag@SiO_2 triangular NPs with a core-shell structure were prepared by treatment of NPs with 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide, 2-(N-morpholino)ethanosulfonic acid, and N-hydroxysuccinimide. The minimum bactericidal concentrations for methicillin-sensitive and methicillin-resistant *S. aureus* were 20 ppm and 350 ppm, respectively for Penicillin G-Ag@SiO_2 [22].

Gentamicin

Gentamicin is mainly employed to inactivate bacteria related to urinary tract infections, sepsis, pneumonia, meningitis, pelvic inflammatory disease, endocarditis, and bone infections [23]. Gentamicin antibiotic could promote the dissolution of poly(N-vinyl-2-pyrrolidone) modified Ag-NPs (Ag-PVP-NPs) resulting in an increased concentration of Ag^+ ions in the bacterial growth medium. Gentamycin reduced the negative charge of the Ag-PVP-NPs to improve their attachment onto the surface of gentamicin-resistant *E. coli*, *E. coli*, and *S. aureus* bacterial cells [24]. Modification of phosphatidylcholine-Au-NPs with gentamycin showed a significant reduction in biofilm mass of *P. aeruginosa* (~0.5) and *S. aureus* (~0.2) in comparison with gentamicin antibiotic alone (~0.6 and ~1) and phosphatidylcholine-decorated AuNPs alone (~0.8 and ~1.5) (Figure 2) [25]. The use of a *Penicillium chrysogenum* filtrate was an eco-friendly and cost-effective method for the biosynthesis of selenium nanoparticles (SeNPs). The combination of Se-NPs with gentamicin antibiotic exhibited prominent anti-planktonic activity producing a zone of inhibition (ZOI) of 20 mm against *Staphylococcus aureus* and a ZOI diameter of 23 mm for *E. coli*. Moreover, this formulation had antibiofilm activity with inhibition values of 85.20%, 87.93%, and 88.67% for *E. coli*, *P. aeruginosa*, and *S. aureus*, respectively [26]. Several antibiotics (trimethoprim, cefotaxime, tetracycline, ampicillin, and gentamicin), as well as the essential oil of *Centaurea damascena* were tested in combination with Ag-NPs, that were biosynthesized by the fungus *Tritirachium oryzae* W5H. The combinations showed significant antibacterial activity against *S. epidermidis*, *S. aureus*, *P. aeruginosa*, and *E. coli*. Among these antibiotics, the gentamicin combination resulted in the greatest antibacterial effect (up to 9-fold higher than gentamycin alone) against *P. aeruginosa* [27].

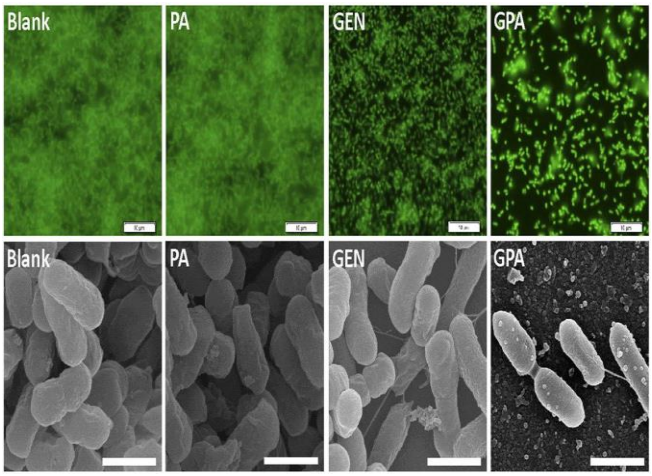

Fig. 2. Reduction in biofilm mass by phosphatidylcholine-decorated Au-NPs (PA), gentamicin antibiotic (GEN), and gentamycin-PA (GPA) (Copyright permission under http://creativecommons.org/licenses/by/4.0/) [25].

Tetracycline

Tetracycline is an antibiotic which can inhibit the protein synthesis of bacteria via blocking the small (30S) subunit of prokaryote ribosomes [28, 29]. In a comparative study, Ag-NPs were combined with tetracycline, enoxacin, kanamycin, neomycin, penicillin, and ampicillin antibiotics. Higher growth inhibition of *Salmonella typhimurium* DT104 was found (up to ~100%) in the case of Ag-NP-tetracycline nanocomplexes at four concentrations 0.5, 2, 8, and 16 μM in comparison with other nanocomplexes such as Ag-NPs, and $AgNO_3$ salt [30]. In comparison to a leaf/flower extract of *Daphne mucronata*, Ag-NPs, amoxicillin-Ag-NPs, and penicillin-Ag-NPs which showed ZOIs of 7.93, 9.9, 15.16, 13.83 mm respectively, tetracycline-Ag NPs showed a higher antibacterial effect with a ZOI of 26.33 mm against *S. aureus.* In this study, *S. aureus* with a thick peptidoglycan cell wall showed a lower sensitivity than *E. coli* with a thin peptidoglycan cell wall. Tetracycline can increase the pore formation in the bacterial cells in combination with the released Ag^+ ions from the Ag-NP surface, thus explaining its synergistic antibacterial mechanism [31].

Polymyxin B

Acinetobacter baumannii is intrinsically carbapenem-resistant thus causing a major public health problem in

the case of patients with immune deficiency [32, 33]. Therefore it is neccessary to discover new effective antibacterial agents against this pathogen. A fungal extract of *Fusarium oxysporum* was used to produce biogenic AgNPs, followed by combination with polymyxin B (an antibiotic clinically used to treat urinary tract infections, sepsis, pneumonia, and meningitis). In comparison to biogenic Ag-NPs with a MBC and MIC of 1.870 and 0.460 µg/mL, respectively, the nano-combination of Ag-NPs-polymyxin B demonstrated a 16-fold reduction of the polymyxin B MIC, and also showed a synergistic antibacterial effect on four out of five strains of *A. baumannii* [34].

Cephalexin

Cephalexin or cefalexin, is a beta-lactam antibiotic related to first-generation cephalosporins, which can inactivate Gram-positive and Gram-negative bacteria by disrupting the bacterial cell wall [35]. This antibiotic is similar to cefotaxime, with the ability to reduce metal ions in order to generate metal NPs. Gold nanoparticles (AuNPs) with spherical, triangular, and hexagonal shapes, and a bimodal particle size distribution of 50-80 nm and 120-200 nm were prepared by reacting different concentrations of chloroauric acid ($HAuCl_4$) and a broad range of concentrations of cephalexin [36]. In a comparative study, the antibacterial activity of combinations of CuO-NPs with 22 different types of antibiotics was evaluated against *E. coli*. The highest synergistic effect was observed for the CuO-NPs-cephalexin combination with increased membrane permeability and cell damage. Surprisingly, they did not find any Cu^{2+} release, cellular uptake of Cu^{2+}, or ROS production, as possible antibacterial mechanisms [37]. The ball milling method may be used to reduce size of bulk materials such as antibiotics, so that nano-cephalexin with improved solubility in water was prepared by ball milling. These antibiotic-NPs showed synergistic effects on *S. aureus* in combination with AgNPs (diameter of <10 nm). When cephalexin-AgNPs were tested at five different weight ratios, including 10-1, 100-10, 500-100, 1000-200, and 5000-500 µg/mL, there were 0, 143.3, 73.4, 52.4, and 50.7 % increases in the zone of inhibition [38]. Various organic or inorganic materials may be used as a linker for coating antibiotics onto the NPs. In this regard, cephalexin was loaded on basil seed mucilage-coated Fe_3O_4 NPs to provide the sustained release of cephalexin (the first 18 h showed a burst release and then a more gradual release for 120 h). The diameter of the ZOIs for this nanoformulation were 17.1, 12.9, 11, and 9.7 mm against *S. aureus*, *Bacillus cereus*, *E. coli*, and *Salmonella typhimurium* respectively, compared to pure cephalexin with values of 13.9, 8.5, 9.6, and 8.5 mm, respectively [39].

Ciprofloxacin

In a comparative study, several antibiotics including penicillin G, amoxicillin, carbenicillin, cephalexin, cefixime, erythromycin, gentamicin, amikacin, tetracycline, ciprofloxacin, clindamycin, nitrofurantoin, nalidixic acid, and vancomycin, were combined with ZnO-NPs with a size range of 20-45 nm to test antibacterial activity against *E. coli* and *S. aureus*. Only the combination of ciprofloxacin (5 µg/disk) with ZnO-NPs (500 µg/disk) showed an increase in the ZOI of 22% and 27% against *E. coli* and *S. aureus*, respectively [40]. Three compounds, including sodium borohydride ($NaBH_4$), tri-sodium citrate dehydrate ($Na_3C_6H_5O_7$), and lactose ($C_{12}H_{22}O_{11}$), were used as reducing and stabilizing agents to prepare Ag-NPs with a size range of 7-85 nm and spherical or prism shapes. The formation of antibiotic-Ag-NPs was mediated by hydrogen bonds between the –OH group of ciprofloxacin and the $–COO^-$ groups of the sodium citrate-functionalized Ag-NPs (Figure 3). There was approximately two-fold higher antibacterial activity for ciprofloxacin loaded Ag-NPs with a prism shape, showing ZOIs of 18 and 21 mm compared to bare NPs with 13 and 12 mm against *E. coli* and *S. aureus*, respectively [41]. Mesoporous NPs have a higher surface area compared with non-porous NPs, and are useful carriers to load antibiotics or other antibacterial agents. Mesoporous iron oxide NPs were functionalized with 3-aminopropyl-triethoxysilane (APTES) to incorporate ciprofloxacin with an incorporation efficiency of 88.23%. *S. aureus* showed disrupted bacterial morphology and a complete loss of biofilm integrity when treated by these NPs at a concentration 50 mg/mL (132.5 µg/mL of ciprofloxacin) [42]. Amine functionalized ZnO-NPs (hexagonal, spherical, or oval shapes with a mean size of 20-26 nm) were prepared and conjugated with ciprofloxacin by

reaction with 3-ethyldimethylaminopropyl carbodiimide and N-hydroxysuccinimide at pH= 8, followed by centrifugation at 5000 rpm for 10 min and drying at 60°C for 120 min. The ciprofloxacin-ZnO-NPs showed 2.7 and 2.9 fold increases in antibacterial activity against *E. coli*, compared to pure NPs and ciprofloxacin, respectively [43].

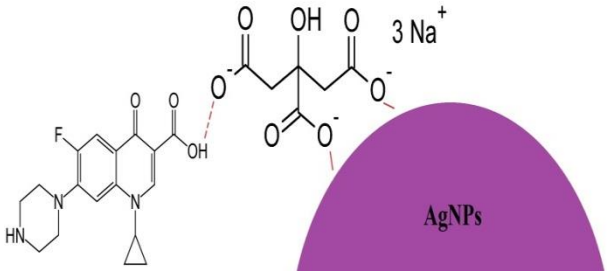

Fig. 3. Probable hydrogen bonding between –OH group of ciprofloxacin with –COO^- groups of sodium citrate-functionalized Ag-NPs [41].

Sulfadiazine and silver sulfadiazine

There are four types of nanomaterials (NMs) classified according to the number of dimensions, zero, one, two, and three dimensional NMs [44]. Graphene oxide is a two-dimensional NM with low stability in aqueous solution, but can be modified with hydrophilic polymers, such as polyethylene glycol (PEG). Sulfadiazine antibiotic is used mainly to treat bacterial meningitis, and infections caused by *Toxoplasma gondii*, *Chlamydia trachomatis*, and *Haemophilus influenzae* [45]. As shown in Figure 4, Ag-NPs and sulfadiazine were loaded onto graphene oxide to prepare hybrid multifunctional NMs with possible triple synergy including capping, puncture, and growth inhibition against *E. coli* and *S. aureus* [46]. Electrospun nanofibers composed of polycaprolactone (PCL) and polyvinyl alcohol (PVA) were used to load Ag-NPs and silver sulfadiazine separately, to increase the flexibility, hydrophilicity, and antibacterial activity of wound dressings. After 30 days, 96% wound closure and significant antibacterial activity against *S. aureus* were observed for Ag-NPs/PCL/PVA, which was higher than PCL/PVA or silver sulfadiazine/PCL/PVA nanofibers [47]. In a similar study, electrospun nanofibers made of zein protein were loaded with silver sulfadiazine at different weight ratios of 0.3, 0.4, 0.5, and 0.6%. The antibacterial effect was significant for 0.6% silver sulfadiazine in comparison to the other ratios against *Bacillus* and *E. coli* [48]. Silver sulfadiazine/nanosuspensions loaded within a P407 thermosensitive hydrogel displayed ZOIs of 4.43, 6.8, and 8.07 mm, compared to silver sulfadiazine/nanosuspensions with values of 6.07, 9.33, and 10.7 mm against *S. aureus*, *E. coli*, and *P. aeruginosa* [49]. Synthetic polymers such as polyacrylonitrile nanofiber mats can be utilized to load silver sulfadiazine. The silver sulfadiazine/polyacrylonitrile nanofiber wound dressings prepared either by electrospinning or immersion, displayed Young's modulus values of 12.613 and 10.153 MPa, and tensile strength of 1.72 and 4.16 MPa, respectively. *Bacillus* and *E. coli* showed higher sensitivity to electrospun and immersion nanofibers compared to polyacrylonitrile [50].

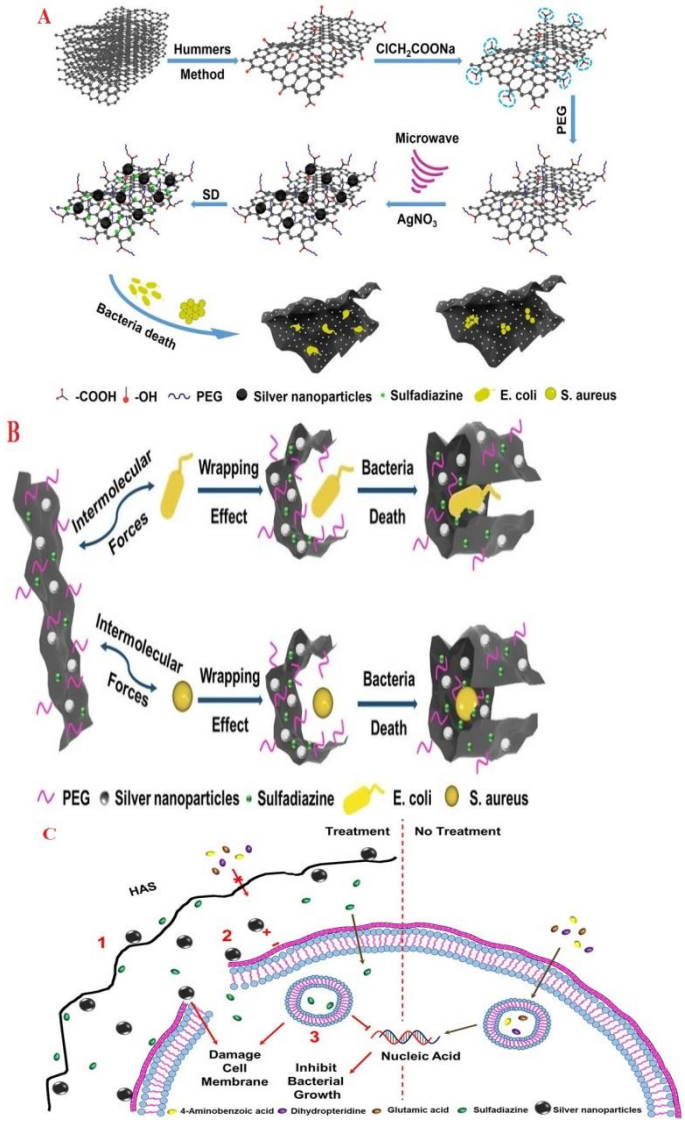

Fig. 4. Loading of Ag-NPs and sulfadiazine onto graphene oxide to provide hybrid multifunctional carriers with

antibacterial mechanisms of capping, puncture, and growth inhibition against *E. coli* and *S. aureus* (Copyright license: http://creativecommons.org/licenses/by/4.0/.) [46].

Conclusions

Metal, metal oxide or metalloid NPs can inactivate bacteria by damaging the bacterial membrane, cell wall, electron transport chain, nucleic acids, proteins or enzymes. This damage can be produced by direct (attachment to biological macromolecules) or indirect (production of ROS) mechanisms. However, the use of the high doses needed for sufficient antibacterial activity can result in poor biocompatibility as well as cytotoxicity in physiological conditions. Additionally, the sustained release of antibiotics in physiological conditions is required in order to heal an infected wound, which may be possible by combining antibiotics with metal, metal oxide, metalloid, or organic/inorganic polymeric NPs. In this way, the surface functionalization of NPs with other antibacterial or biocompatible agents is an important approach. Antibiotics can be used to provide synergistic antibacterial effects with metal or metal oxide NPs at safe low-doses. A potential strategy to overcome antibiotic resistance is the synergistic effects between antibiotics and NPs, which can inhibit bacteria over a long period of time. In addition, the dual effect of some antibiotics, for example gentamicin, can be increased by using its dispersion in poly(N-vinyl-2-pyrrolidone) modified Ag-NPs (Ag-PVP-NPs), leading to increased concentrations of Ag+ ions in the bacterial medium, and the attachment of the Ag-PVP-NPs onto the bacterial surface.

The sustained release of metal ions from micro or nano-formulations of metal or metal oxide NPs, in combination with antibiotics, is an important factor to explain the synergistic antibacterial activity. However, in the case of Gram-negative bacteria, an increase in ROS generation and the endocytosis of CuO-NP-cephalexin were not found to explain the antibacterial activity, whereas the synergistic activity was based on damage to the bacterial membrane. Furthermore, some antibiotics such as cefotaxime and cephalexin are able to act as reducing agents to prepare stabilized metal NPs from metal ions. More research into the synthesis procedures, and the synergistic activity of metal, metal oxide, or metalloid NPs combined with antibiotics, especially against antibiotic-resistant bacteria, should be conducted in future studies.

Study Highlights

- The ROS production is main antibacterial and anticancer mechanism of metal or metal oxide NPs.
- Functionalization of metal, metal oxide, and metalloid NPs by biocompatible polymers to obtain low cytotoxicity.
- Antibiotics and anticancer drugs can be used to modify metal, metal oxide, and metalloid NPs.

Abbreviations

ESBL: Extended spectrum beta-lactamase
MDR: Multidrug-resistant
MRSA: Methicillin-resistant *S. aureus*
NPs: Nanoparticles
PCL: Polycaprolactone
PVA: Polyvinyl alcohol
PVP: Poly(N-vinyl-2-pyrrolidone)
ROS: Reactive oxygen species
ZOI: Zone of inhibition

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Authors' contribution

MA: conceptualization, writing, and drafting of the manuscript; MRH, FM, JFK, and HK: revising of the manuscript.

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