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Nanoantibiotics: Future nanotechnologies to combat antibiotic resistance

Saima Muzammil[1], Sumreen Hayat[1], M. Fakhar-e-Alam[2,3] Bilal Aslam[1], Muhammad Hussnain Siddique[4], Muhammad Atif Nisar[1,] Muhammad Saqalein[1], Muhammad Atif[5,6], Ayesha Sarwar[1], Anwaar Khurshid[7], Nasir Amin[3], Zhiming Wang[2]

[1]Department of Microbiology, Government College University, Allama Iqbal road, 38000, Faisalabad, Pakistan, [2]Institute of Fundamental and Frontier Science, University of Electronic Science and Technology of China, 610054 Chengdu, China, [3]Department of Physics, GC University, 38000, Faisalabad, [4]Department of Bioinformatics and Biotechnology, Government College University, Allama Iqbal road, 38000, Faisalabad, Pakistan, [5]Department of Physics and Astronomy, College of Science, King Saud University, Riyadh, Saudi Arabia, [6]National Institute of Laser and Optronics, Nilore, Islamabad, Pakistan, [7]Quaid e Azam Medical College Circular Road, 63100, Bahawalpur

TABLE OF CONTENTS

1. ABSTRACT

The discovery of antibiotics was hailed as a historic breakthrough for the human race in the fight against bacterial and malignant infections. However, in a very short time, owing to their acute and aggressive nature, bacteria have developed resistance against antibiotics and other chemotherapeutics agents. Potentially, this situation could again result in bacterial infection outbreaks. Metal and metal oxide nanoparticles have been proven as better alternatives; the combination of antibiotics and metal oxide nanoparticles was shown to decrease the toxicity and enhance the antibacterial, antiviral, and anticancer efficacy of the agents. This review provides a detailed view about the role of metal and metal oxide nanoparticles in the treatment of infections in conjunction with antibiotics, their modes of action, and synergism. In addition, the problems of multidrug resistance are addressed and will allow the development of a comprehensive, reliable, and rational treatment plan. It is expected that this comprehensive review will lead to new research opportunities, which should be helpful for future applications in biomedical science.

2. INTRODUCTION

During the 19th century, infectious diseases were a major cause of human mortality. However, the discovery of antibiotics in the first quarter of the 20th

century led to a phenomenal success and shifted the balance to a substantial reduction in the number of deaths resulting from infections, but unfortunately this trend was short lived; within approximately half a century, we are again losing the battle as microbes develop resistance to the currently available antibiotics, partly owing to the irrational use and abuse of antibiotics (1,2). The pace of development of new and more effective drugs is very slow and, thus, many problems have arisen during the treatment of diseases. The passage of time has led to a gradual increase in microbial resistance against existing antimicrobial agents, which now has become a major global threat to the human race. Moreover, several studies have indicated that more than 70% of infections caused by bacteria are resistant to one or more antibiotics commonly used to eradicate these infections (3). Therefore, it is of paramount importance to identify novel and efficient antimicrobial therapies to circumvent the problems of global resistance of human pathogens to antimicrobial agents.

Since prehistoric times, metals such as zinc (Zn), copper (Cu), gold (Au), titanium (Ti), and silver (Ag) have been used for therapeutic purposes because of their broad-spectrum activities against a number of microorganisms (4). Recent advances in the field of nanotechnology have confirmed the importance of these metals, and nanoparticles (NPs) that exhibit antimicrobial properties have gained substantial scientific recognition as potent inhibitory agents for the growth of pathogens. To conquer the drug resistance phenomena of microbes, NPs exhibit multifunctionalities, such as the enhancement of intracellular accumulation of antimicrobial agents or the inhibition of biofilm formation (2,5,6). Various metal and metal oxide NPs, such as titanium dioxide (TiO_2), silver oxide (Ag_2O), copper oxide (CuO), zinc oxide (ZnO), gold (Au), silicon (Si), magnesium oxide (MgO), and calcium oxide (CaO), have been characterized for their efficient antimicrobial activities.

The antimicrobial efficacy of metal oxide NPs is mainly attributed to the large surface area, which ensures that a wide range of reactions with bio-organics is available on the surface of cell (7). The smaller the particle, the larger surface area to volume ratio it will have; thus, the augmentation of its chemical and biological activities can be enhanced by an increased area of contact of a metal with a microbe. The use of nanoscale metals has achieved a hundred-fold reduction in concentration with a simultaneous increase in antimicrobial properties; the reduction of the particle size from 10 μm to 10 nm increases the surface area of contact by a factor of 10^9 (8).

Nevertheless, there are a number of safety concerns associated with metallic and metal oxide NPs, such as circulatory problems, respiratory and neurological disorders, and other toxicity issues (9-11). However, various types of NPs are still considered to be non-toxic and are used to reduce the toxicity hazards of other therapeutic agents (12).

The precise mechanism of the antimicrobial action of metal oxide NPs is not yet clear. However, two alternative possibilities have been suggested: (a) free metal ion toxicity arising from the dissolution of the metals from surface of the NPs; and (b) reactive oxygen species (ROS) on the surface of the NPs that cause oxidative stress (13).

Various studies have indicated that high doses of bactericidal antibiotics resulted in biochemical and genetic alterations in the body along with the generation of highly toxic oxidative radical species (14). Therefore, in order to mitigate the problems associated with these bactericidal agents, multimode therapeutic agents are required (15). Various studies have demonstrated that the combination of polymeric or metallic NPs with standard antibiotics not only increased the bactericidal activity of both therapeutic agents, but also reduced the associated toxicity of both agents toward the human body. This combination therapy also restored the ability of conventional antibiotics to destroy drug-resistant bacteria. Another advantage offered by combination therapies is the enhanced concentration of antibiotics at the antibiotic-bacterium site of interaction. Numerous studies have been conducted to show the synergistic effect of metallic NPs and conventional antibiotics to kill or reduce the growth of pathogens; these are summarized in Table 1.

The primary focus of this review will be the utilization of metal and metal oxide NPs as potential therapeutic agents having synergistic activity with antibiotics and evaluation of their modes of action. Meanwhile, the limitations of this combination therapy for the eradication of the infections caused by drug-resistant bacteria and the possible reduction in the toxic potential of these agents, compared with their individual use, will also be discussed.

2.1. Mechanism of action of NPs

Although the exact mechanisms of action of metal and metal oxide NPs are not fully understood, a number of hypotheses have been proposed. These include the physical disruption of cell structures, generation of ROS (reactive oxygen species) and antioxidant depletion, protein dysfunction, membrane impairment and interference with nutrient assimilation, alteration of signal transduction by dephosphorylation of the peptide substrates on tyrosine residues, which results in the inhibition of signal transduction and suppression of bacterial growth (16-18).

NPs have the potential for direct interaction with the bacterial cell wall and ZnO or AgNPs can penetrate the cell wall to cause changes in the

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Table 1. Examples of synergy between metallic nanoparticles and antibiotics

Nanoparticles	Antibiotics used	Microorganisms tested	Conditions	Effect	References
	Doxycycline	*Klebsiella pneumoniae*	37 °C for 24 h, size of AgNPs less than 50 nm	Synergistic effect was observed for doxycycline + AgNP compounds.	(44)
	Gentamicin and neomycin	*Staphylococcus aureus*	37 °C for 24 h, 10 µg of AgNPs used	AgNPs + G and AgNPs + N showed synergistic effects in 50% and 45% of the strains respectively. Meanwhile, 15% and 45% reduction in resistance has been observed to gentamicin and neomycin respectively.	(48)
	Ampicillin, kanamycin, erythromycin, and chloramphenicol	*Salmonella typhi, Escherichia coli, S. aureus,* and *Micrococcus luteus*	35 °C for 24–48 h, 5 to 40 nm size of AgNPs	Overall synergistic antibacterial effect observed: 18.9.6%, 27.9.3%, 18.1.3%), 74.8.9% with AgNP for erythromycin, kanamycin, chloramphenicol, and ampicillin respectively.	(50)
Silver nanoparticles (AgNPs)	β-Lactam, cefotaxime	*Staphylococcus arlettae* (AUMC b-163), *Escherichia coli* (ATCC 8739), *Staphylococcus aureus* (ATCC 6538P)	35 °C for 24 h for bacterial strains. Equal volumes of freshly prepared AgNPs and bacteria were used (25 µL).	Synergistic effects: 85.1.4%, 17.2.7%, 13.5.4% for *S. arlettae, E. coli*, and *S. aureus*, respectively.	(150)
	Ampicillin, chloramphenicol, and kanamycin	*Staphylococcus aureus* (ATCC 25923), *E. coli O157* (ATCC 43895), *E. coli* (ATCC 25922), *and Pseudomonas aeruginosa* (ATCC 27853)	37 °C for 24 h	Overall synergistic effects have been observed for both Gram positive and Gram negative.	(51)
	Penicillin G	*Actinobacillus pleuropneumoniae* (R)	At 37 °C for 24 h and pH 7.4., 2 µg/mL Penicillin G with 6.3. µg/mLAgNP (8 nm)	Synergistic effect was observed for Penicillin G combined with AgNPs (8 nm).	(39)
	Tetracycline and neomycin	*Salmonella typhimurium* DT104 (multi-drug resistant)	25 °C for 2 h. AgNPs (5 µg/mL) with tetracycline hydrochloride (1.2.5 µg/mL) and neomycin sulfate (1.2. µg/mL)	Significantly more inhibition was observed with neomycin and AgNPs conjugate and 4.8.-fold increase in MIC with tetracycline and AgNPs	(115)
	Beta-lactam: cephem (Cephalothin and Cefazolin)	*Bacillus subtilis, S. aureus,* and *Micrococcus luteus*	35 °C for 24–48 h, 14 nm size	Both of the cephem antibiotics (cephalothin and cefazolin) showed a maximum increase of 30% in combination with 20 µg/mL AS-AgNPs against *Bacillus subtilis* and *Micrococcus luteus* and 3.5.7% for *S. aureus*	(152)
Bismuth nanoparticles (BiNPs)	Ciprofloxacin, norofloxacin, tetracycline, and metronidazole	*Klebsiella pneumoniae*	37 °C and 24 h. 1750 ppm/mL bismuth nanoparticles, Size, 200 nm plus 2048 µg/mL of antibiotic	Synergistic effect was observed between all antibiotics and BiNPs.	(74)
	Cefotaxime, ampicillin, ceftriaxone, cefepime	*E. coli, K. pneumoniae, S. paucimobilis,* and *P. aeruginosa*	37 °C for 24 h. 240–0.0.01 µg/mL antibiotics and 0–120 µg/mL for ZnO NPs used	Significant decrease in MIC decrease with cefotaxime and ZnO NPs against *K. pneumoniae* (85.7.%), *S. paucimobilis* (50%), *P. aeruginosa* (70%), and *E. coli* (50%) have been observed. Meanwhile decrease in MIC due to ZnO NP with other antibiotics also have been observed.	(83)
	Norfloxacin, Ofloxacin and Cephalexin	*Pseudomonas aeruginosa* (ATCC 10145), *Escherichia coli* (ATCC 21210)	37 °C for 24 h. 0.1. mg/mL of each antibiotic with 100 µg/mL NPs	Significant increase of inhibition zone of antibiotics with ZnONPs have been observed against all isolates.	(84)

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Zinc nanoparticles (ZnO NPs)	Ceftriaxone	*E. coli* (TOP10)	37 °C for 24 h, 0.5. mg/L ceftriaxone and 0.0.3125 mg/L. Size of nanorods, 15–22 nm.	Synergistic antibacterial effects against *E. coli* have been observed by ZnO nanorods with ceftriaxone.	(86)
	Ciprofloxacin	*S. aureus* and *E. coli*	35 °C for 18 h, 20–45 nm size, and 500 µg/ disk used	A total of 27% and 22% increase in inhibition zones was observed for ciprofloxacin in the presence of ZnO NPs in *S. aureus* and *E. coli*, respectively	(87)
	Beta lactams, amino glycosides, and azolides	*S. aureus*	37 °C for 24 h, 100 µg/ disc of zinc oxide are used, size 80 nm	The highest increase was observed for penicillin G and amikacin, i.e., 10 mm increase in the zone of inhibition, whereas for clarithromycin, 2 mm increase had been observed	(85)
Titanium nanoparticles (TiO_2NPs)	Penicillin G, amikacin, cephalexin, cefotoxime	Methicillin-resistant *S. aureus* (MRSA)	30 °C for 24 h, 20 nm size of titanium dioxide nanoparticles, and 10 µg/discs was used	10 mm increase in zone size. TiO2 nanoparticles significantly improved antibiotic efficacy against *S. aureus* when combined with beta lactams, cephalosporins, and aminoglycosides	(101)
	Gentamycin, vancomycin	*Staphylococcus epidermidis* and *Staphylococcus haemolyticus*	30 °C for 24 h, 20 µg/ disc of AuNPs, and 12–32 nm size	0.3.1 mm increase in fold area for vancomycin against *S. epidermidis* and 0.1.7 mm increase in gentamicin against *S. haemolyticus*	(66)
Gold nanoparticles (AuNPs)	Ampicillin, streptomycin, and kanamycin	*E. coli DH5a, M. luteus,* and *S. aureus*	37 °C for 24 h, AuNPs size, 14 nm	15%, 12%, and 34% increase in inhibition zone for *E. coli* with A/S/K+Au NPs respectively; 20%, 109%, and 18% increase in inhibition zone for *M. luteus* A/S/K+AuNPs respectively; 12% and 34% increase in inhibition zone for S. aureus with A/ K+AuNPs, respectively.	(153)
	Beta lactams: cefaclor	*S. aureus* and *E. coli*	37 °C for 24 h and 22–52 nm size and 500 mg/ mL of AuNPs used	MICs of cefaclor reduced gold nanoparticles were 10 mg/mL and 100 mg/mL for *S. aureus* and *E. coli* respectively.	(68)
Iron Oxide nanoparticles (Fe3O4NPs)	Streptomycin	*S. aureus* (ATCC 6538), *B. subtilis* (ATCC6633), *E. coli* (ATCC 25922), *and P. aeruginosa* (ATCC9027	37°C for 24 h, size of nanoparticles used = 18nm	Zones of inhibition at concentrations (10, 20, 40, and 80): *S. aureus* (15 mm, 14 mm, 17 mm, 20 mm), *B. subtilis* (14 mm, 16 mm, 17 mm, 21 mm), *E. coli* (12 mm, 14 mm, 15 mm, 17 mm), *P. aeruginosa* (13 mm, 14 mm, 15 mm, 18 mm)	(112)
	Kanamycin and rifampicin	*Bacillus cereus* (ATCC 3061), *E. coli* (ATCC 43890), *Listeria monocytogenes* (ATCC 19115), *and S. aureus* (ATCC 6538)	25 µg Fe3O4 nanoparticles + 5 µg (kanamycin and rifampicin)	Kanamycin formed inhibition zone against all pathogens, whereas rifampicin formed inhibitory zone against *S. aureus* only.	(113)
	Amoxicillin	*E. coli* and *S. aureus*	37 °C for 24 h, Cu NPs (3–40 nm)	A total of 9.9.% and 8.9.% increase in inhibitory effect observed in the presence of Cu NPs for *E. coli* and *S. aureus* respectively.	(139)
Copper nanoparticles (CuNPs)	Tetracycline and kanamycin	*B. subtilis* and *P. fluoresence*	37 °C for 24 h, CuNPs (11.8. nm)	30% increase in biocidal activity of tetracycline against *B. subtilis*, 3% increase in activity of kanamycin against *B. subtilis* and 20% for *P. fluoresence*	(37)
	Amikacin, ciprofloxacin, gentamicin, norfloxacin	*E. coli, P. aeruginosa, Klebseilla spp. S. aureus*	37 °C for 24 h	At 60 mg/mL, 18 mm for *E. coli*, 16 mm for *Klebsiella*	(147)

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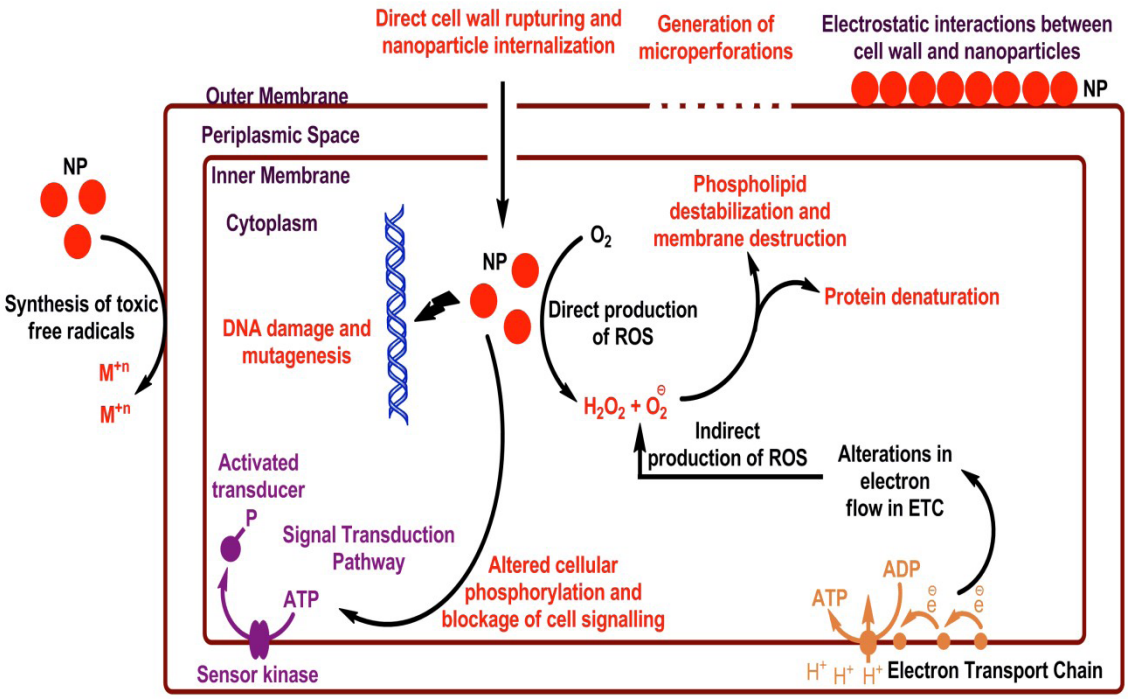

Figure 1. Possible mechanisms of action of metallic nanoparticles causing gram negative bacterial cell death.

bacterial cell membrane, causing structural damage, loss of membrane integrity, and ultimately, cell death (19-22). NPs also cause pit formation in the bacterial cell wall; for example, AgNPs accumulate on the cell surface and form pits in the cell wall (23).

AuNPs exert their antibacterial activities through disintegration of the membrane potential, a decrease in ATP level by inhibiting ATPase activity, or inhibition of the subunit of ribosome from binding to transfer RNA (tRNA) (24).

Another possible mechanism involves the production of free radicals, which result in the generation of oxidative stress. The generated ROS can permanently damage bacteria, such as by destroying mitochondria, DNA, and membrane, ultimately causing cell death (25,26). The bacterial cells may need to upregulate ROS detoxification enzymes to resist lethal doses of these elements (27). The oxidation of cellular thiols is an important factor in oxidative stress, which results in the generation of protein disulfides and exhaustion of antioxidant reserves, especially glutathione, within microbial cells (28). Metal NPs also have the ability to interact with sulfur- and phosphorus-containing biomaterials present in bacterial cells, e.g., DNA bases. These can act on soft bases and destroy DNA, which results in cell death (29). Some possible modes of action for the NP-induced destruction of bacterial cells and subsequent cell death are shown in Figure 1.

3. ANTIBIOTIC-CONJUGATED METAL AND METAL OXIDE NPs

3. 1. AgNPs

Ag and its compounds have long been recognized for their antimicrobial activities. During the early 19th century, Carl Crede (a German obstetrician) used silver nitrate for the cure and prevention of microbial infections, but owing to the discovery of penicillin, the microbicidal applications of Ag have gradually diminished (30). Owing to the current diminished efficacy of conventional drugs, the use of Ag for the treatment of infections has regained importance (31). Ag is a non-hazardous, safe inorganic antibacterial agent used for centuries and has the ability to kill approximately 650 different types of disease-causing microorganisms (32). AgNPs were found to be effective even at very low concentrations (mg/L), but no cytotoxicities to eukaryotic cells, including human erythrocytes, have been reported (33,34). AgNPs do not have a specific bactericidal effect, so the risk of development of resistance is not as high as for antibiotics.

The bactericidal properties of AgNPs (nanosilver) have been evaluated by many researchers against different microorganisms, such as *Escherichia coli* (strains MTCC 443, MTCC 739, and ATCC 25922), *Bacillus subtilis* (strain MTCC 441), *Proteus mirabilis* (MTCC 442), *Staphylococcus aureus* (strains NCIM

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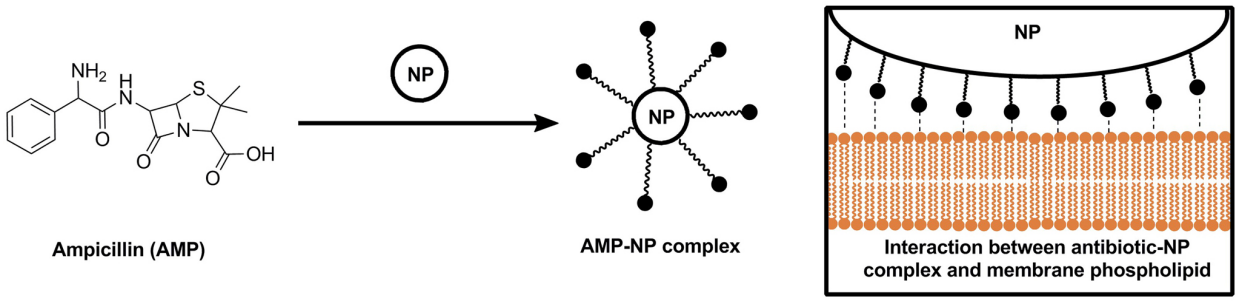

Figure 2. Ampicillin structure and binding of silver nanoparticles chelated with antibiotics and the interaction between the ampicillin-NP complex and the bacterial phospholipid membrane.

2079 and ATCC 25923) and *Pseudomonas aeruginosa* (MTCC 424) (23,35-38). Strain specificity has been observed for different microorganisms (35,39) and more pronounced effect was observed against Gram-negative bacteria in comparison to that against Gram-positive bacteria (18).

In the last decade, the use of nanosilver combinations with different antibiotics has rapidly increased (40). Owing to the numerous attributes of conformational entropy in polyvalent binding, nanosilver was able to bind to flexible polymeric chains of antibiotics (41,42). Furthermore, nanosilver has chemical stability, well-developed surface chemistry, and appropriate size (20 nm in diameter, which is 250 times smaller than the size of the bacterium); nanosilver has the ability to maintain a constant size and shape in solution. Therefore, it shows potential for use as an inorganic nanomaterial in combination with different antibiotics (43). In the literature, synergistic effects of nanosilver and different classes of antibiotics have been discussed. Kumar *et al.* demonstrated the synergistic effect of AgNPs with doxycycline against *Klebsiella pneumoniae.* Doxycycline is known to block cell division and AgNPs are assumed to disrupt cell wall with a deleterious effect on nitrogenous bases and cellular proteins. In this case, a doxycycline-AgNP complex is formed, i.e., AgNP is covered by doxycycline, and the antibacterial effects were enhanced by this combination in comparison with those of doxycycline and AgNPs alone (44).

The conjugation effects of AgNPs on many groups of antibiotics with different modes of action, such as ciprofloxacin, imipenem, gentamycin, vancomycin, neomycin, imipenem, and trimethoprim, have been evaluated and were found to be more effective (45-48). A remarkable synergistic effect against *P. aeruginosa* was observed with AgNPs and vancomycin or chloramphenicol; 4.9.-fold and 4.2.-fold increases in zone diameter were recorded for chloramphenicol and vancomycin, respectively. Additionally, a 11.8.-fold increase in the zone diameter of streptomycin was observed when combined with AgNPs against *E. coli*, which confirmed the synergistic action of antibiotics conjugated with AgNPs (49).

It has been reported that in the presence of AgNPs, the antibacterial activity of erythromycin, kanamycin, ampicillin, and chloramphenicol was enhanced against *E. coli, Salmonella typhi, S. aureus*, and *Micrococcus luteus*. Ampicillin showed the largest increase, followed by kanamycin, erythromycin, and chloramphenicol (50). Thus, AgNPs have been demonstrated as a promising antibacterial tool in conjugation with antibiotics in the medical field.

The mechanism involved in the antibacterial activities of AgNPs and their synergism is the production of hydroxyl radicals and impairment of the function of important protective factors. In the presence of conventional antibiotics, this synergism likely decreases the viability of bacterial strains at reduced concentrations of antibiotics (51). The bonding reaction between the antibiotic and AgNPs may increase synergistic activity. Many active groups, such as amino and hydroxyl groups, are present in antibiotic molecules, which react easily with AgNPs by chelation, as shown in Figure 2**.** Another study reported that Ag chelation prevented the unwinding of DNA and thus exhibited a bactericidal effect (52).

3.2. AuNPs

The practice of using Au in Chinese medicine originated from approximately 2500 BC. In Indian Ayurvedic medicine, red colloidal Au is still used for regeneration and revival in old age under the name of Swarna Bhasma (“Swarna” means gold, “Bhasma” means ash) (53). AuNPs are considered as strong candidates for antibacterial agents, but have been also been widely used for cancer therapies (54,55). The antibacterial activities of AuNPs are well established against many microorganisms e.g., *Bacillus Calmette-Guérin* (BCG), methicillin-resistant *S. aureus* (MRSA), *E. coli,* and *S. typhi* (56-59). The efficacy of the antibacterial activity of AuNPs can be improved by the addition of antibiotics; AuNPs can act as carriers or vehicles for antibiotics and subsequently enhance the bactericidal effect of the antibiotics (5,60).

AuNP conjugates have been reported to exhibit enhanced bactericidal activity against Gram-

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negative and Gram-positive bacteria (61). Payne *et al.* synthesized kanamycin-conjugated AuNPs (Kan-AuNPs) using 1.7.2 mM kanamycin sulfate with M9 minimal media buffer and evaluated their antibacterial effects against Gram-negative and Gram-positive bacteria. The MIC of kanamycin in Kan-AuNPs against *P. aeruginosa* PA01 showed a 7.5.-fold decrease and in the case of *S. bovis*, a 52.2.-fold decrease in MIC was observed. Similarly, vancomycin-coated AuNPs exhibited enhanced antimicrobial activity against vancomycin-resistant enterococci (VRE) (62). There has been a recent disturbing rise in the number of vancomycin resistant organisms, which has resulted in the development of new techniques to boost the *in vitro* antibacterial potential against them (63). Vancomycin and vancomycin-bound gold NPs (VBGNPs) exhibited remarkable antibacterial activity against vancomycin-sensitive *S. aureus* (VSSA) and simultaneously vancomycin alone exhibited very low antibacterial activity against vancomycin-resistant *S. aureus* (VRSA) owing to the differences in the composition of the terminal peptides of the VRSA from those of VSSA. Instead of binding to the terminal peptides, the VBGNPs bind to the transpeptidase of the glycopeptidyl precursors present on the cell surface of VRSA and successfully lyse the cell wall of VRSA. Conversely, the growth of *E. coli* was not considerably influenced by vancomycin alone. The VBGNPs showed significant antibacterial activity against *E. coli*. Moreover, these VBGNPs were efficiently collected in the outer membrane and some significantly invaded the cells. The binding of vancomycin molecules with high affinity and specificity to the C-terminal L-lysyl-D-alanine portion of peptidoglycan precursors is prohibited by the outer membrane of Gram-negative bacteria. VBGNPs effortlessly move through the outer and inner membrane of *E. coli* cells and may disrupt the integrity of the lipopolysaccharide membrane, which leads to a considerable increase in the permeability of VBGNPs. Ultimately, vancomycin can easily bind with the mucopeptide portion, which results in cell wall lysis (61). When coated with AuNPs, the aminoglycosidic antibiotics, such as streptomycin, gentamycin, and neomycin, exerted antibacterial effects against various Gram-positive and Gram-negative bacteria (64,65). Roshmi *et al.* monitored the effect of AuNP-based antibiotic conjugates on biofilm-forming *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* and identified a 0.3.1-fold increase in the case of the vancomycin-AuNP conjugate against *S. epidermidis* and a 0.1.7-fold increase in the case of the gentamycin-AuNP conjugate against *S. haemolyticus*. Additionally, vancomycin-AuNPs decreased the MIC from 62.5. to 15.6.5 µg/mL of vancomycin against all *S. epidermidis* isolates and gentamycin-AuNPs reduced the MIC from 125 to 31.2.5 µg/mL; thus, the efficiency of both antibiotics was improved (66). However, Burygin *et al.* studied the combination of gentamicin with 15-nm colloidal AuNPs on *E. coli* and observed no significant differences between the antibacterial activity of gentamycin alone and in combination with the AuNPs. The author explained that antibiotic-NP aggregate was unable to penetrate into the agar well; he also suggested that antibiotic concentration should be high enough to cover the NPs in case AuNPs do not possess antimicrobial activity, but they could act as drug carriers and enhance the bactericidal effect of antibiotics (60). In another study, Chamundeeswari *et al.* observed a two-fold increase in the antimicrobial potential of chitosan-capped AuNPs conjugated with ampicillin (C-AuNp-Amp) in comparison with free ampicillin (67).

The antibacterial activity of cefaclor-reduced AuNPs has been investigated against *S. aureus* and *E. coli*. The MICs obtained against *S. aureus* were 10 mg/mL from cefaclor reduced-AuNPs and 50 mg/mL from cefaclor, which confirmed the enhanced antibacterial activity of cefaclor when combined with AuNPs. The amine group of cefaclor worked as both a capping and a reducing agent and, subsequently, the existence of the free β-lactam ring on the surface of the NPs preserved the antibacterial activity of cefaclor. The synthesis of the peptidoglycan layer was inhibited by cefaclor, making the cell walls spongy. Moreover, the AuNPs produced perforations in the cell wall that resulted in the discharge of cellular contents and, ultimately, cell death. It is also suggested that AuNPs bind to bacterial DNA and restrain the unwinding and transcription of DNA (68).

3.3. Bismuth NPs (BiNPs)

Bi is a delicate crystalline metal with a high level of magnetism; it is generally used as bismuthinite (bismuth sulfide), bismuth oxide, and bismuth carbonate (69). Bismuth oxide NPs exhibit potent antibacterial properties and good biocompatibility as a potential drug carrier (70,71). The antibacterial activities of BiNPs alone have been reported in literature (72-73), but only a few reports describe the synergistic effect of BiNPs with antibiotics. Tarjoman *et al.* studied the synergism with antibiotics including tetracycline, ciprofloxacin, norofloxacin, and metronidazole against *K. pneumoniae* isolates carrying the PKS gene, which encodes for colobactin and induces colorectal cancer. When used in conjugation with antibiotics, BiNPs exhibited synergistic activities. BiNPs demonstrated very low toxicity in comparison with other heavy metal NPs (74).

3.4. ZnONPs

ZnO oxide has been granted “generally recognized as safe” (GRAS) status by the U.S. Food and Drug Administration. As a food additive, it is most frequently used as a Zn source in cereal-based foods. ZnO has been incorporated into the linings of food cans, in packaging for meat, fish, corn, and peas to preserve colors, and to prevent spoilage because of its antimicrobial efficacy (75,76). The antibacterial activity is further enhanced by the use of nanosized particles (77). ZnONPs also exhibit bactericidal properties

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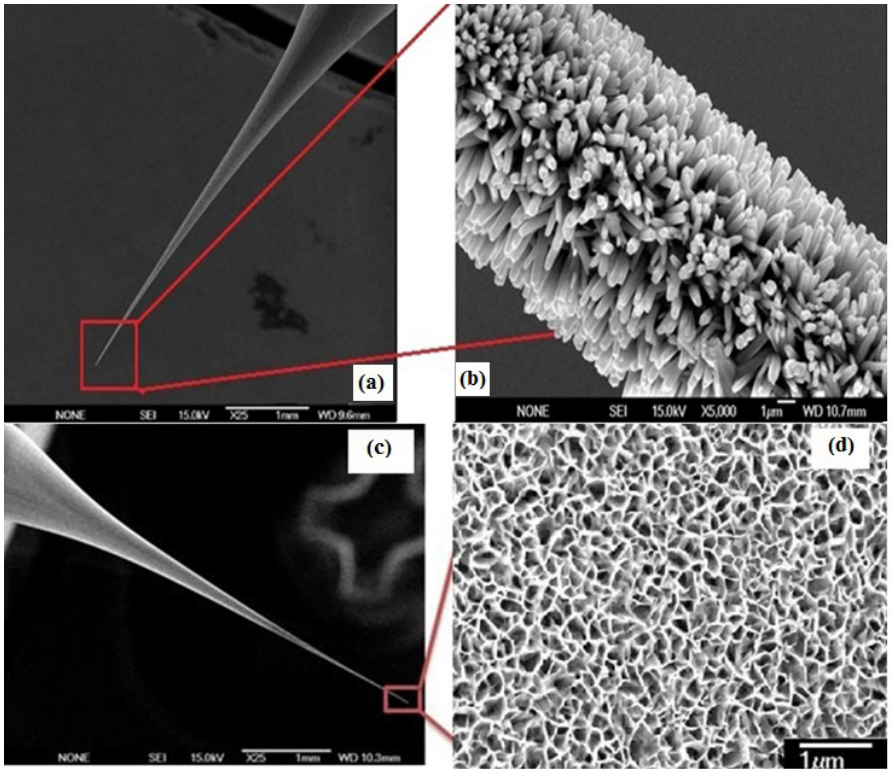

Figure 3. Various morphologies of ZnO nanostructures: (a) Zinc oxide nanorods (ZnO NRs); (b) ZnO NRs grown form amplified form of SEM representation; (c) Zinc oxide nanoporous (ZnO Nps); and (d) amplified form of ZnO Nps.

via multiple mechanisms including photo-oxidation and photocatalysis (76,78). To tackle drug-resistant bacteria, ZnONPs with a diameter of approximately 19 nm can be used against strains of Enterobacteriaceae, in particular *K. pneumoniae* and *E. coli*, which show extended spectrum β-lactamase (ESBL)-mediated resistance to third-generation cephalosporins (79,80). Numerous studies of the antibacterial effect of ZnONPs against different microorganisms such as *S. aureus, B. subtilis, S. epidermidis, Pseudomonas* spp.*, Acinetobacter spp.*, and *Proteus* spp. have been reported (79,81).

The mechanism of action includes the initiation of intracellular generation of ROS, which can ultimately cause cell death, and has been considered as a major action of ZnONPs. The mechanical destruction of the cell wall can occur through the release of Zn^{2+} ions and attachment to the cell membrane. ZnONPs can act as an elegant weapon against multidrug-resistant microorganisms and offer a competent alternative strategy to antibiotics (82).

The increased synergistic bioactivity of ZnONPs with β-lactam antibiotics was observed against a group of clinically isolated extended spectrum β-lactamase producers (ESBL) (e.g., *K. pneumoniae, P. aeruginosa*, *E. coli*, and *S. paucimobilis*) associated with urinary tract infections. A maximum increase of 85.7.1% in the zone of inhibition has been observed with the conjugated effect of ZnONPs and cefotaxime (83). ZnONPs integrated with the antibiotics (ofloxacin, norfloxacin, and cephalexin) exhibited improved activity against *P. aeruginosa, S. aureus and E. coli* (84). Moreover, Namasivayam *et al.* reported inhibition of *P. aeruginosa* and *S. aureus* biofilms by ZnONPs in combination with ofloxacin, norfloxacin, and cephalexin. The synergistic role of ZnONPs was investigated with more than 25 different antibiotics against *E. coli* and *S. aureus*. (84). The results obtained by different researchers revealed that ZnONPs could exert a positive effect on the antibacterial activities of penicillins, cephalosporins, aminoglycosides, glycopeptides, macrolides, lincosamides, gentamicin, clarithromycin, ofloxacin, ceftriaxone, and tetracycline (85,86).

ZnONPs can act as potential drug carriers to overcome increasing antibiotic resistance, may be regarded as a significant adjuvant in the combined therapy of ampicillin, cefotaxime, cefepime, and ceftriaxone, and appear to exert greater damage by causing mechanical destruction to the cell membrane. The synergistic effect of ZnONPs with different antibiotics was tested against *S. aureus* and *E. coli*. The antibacterial activity of ciprofloxacin against both strains was enhanced in the presence of ZnONPs. ZnONPs may be regarded as a potential adjuvant in the conjugation therapy of ciprofloxacin owing to their significant synergistic effect with ciprofloxacin (87). The mechanism of the synergism suggested that ZnONPs might hinder the pumping activity of the protein NorA, which is involved in the active efflux of fluoroquinolones

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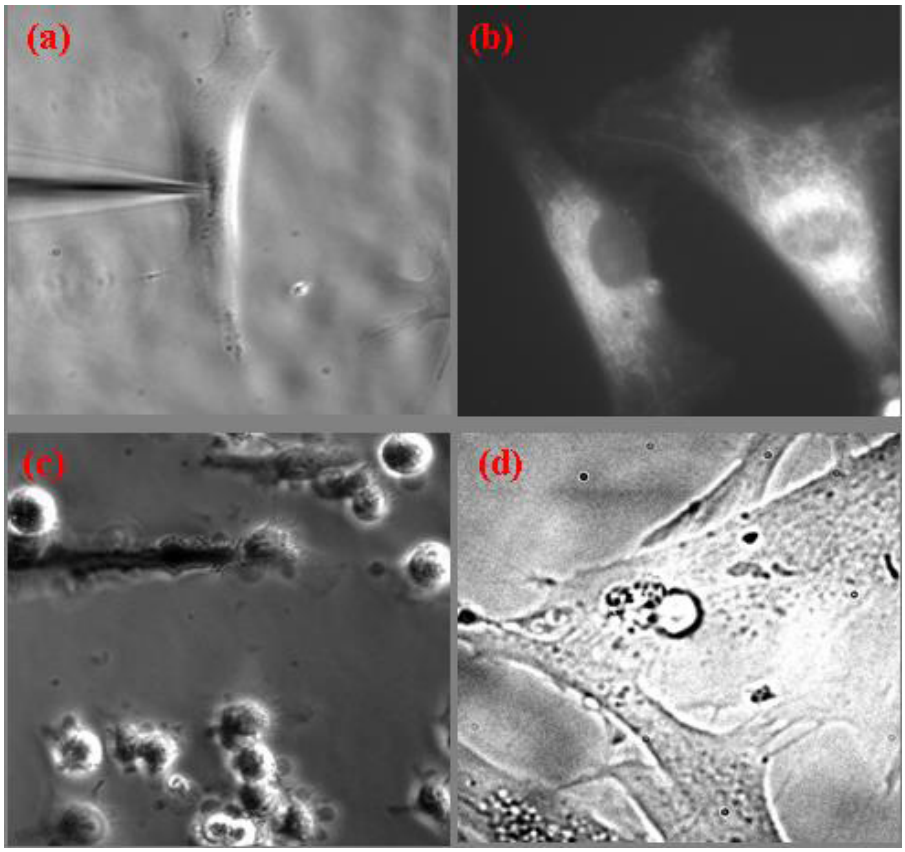

Figure 4. Insertion of femtotip capillary superficial layer grown with (a) ZnO nanowire complex with PpIX towards foreskin fibroblast; (b) indigenous fluorescence after ZnO NWs exposure towards foreskin fibroblast cell model; (c) Cell killing structure after ROS production as a resultant of ZnONW complex with PpIX femtotip capillary insertion after UV exposure via loss of mitochondria; (d) ill-defined morphology of foreskin fibroblast cells after photodynamic reaction and production of necrosis.

from the bacterial cell to confer resistance against the antibacterial effects of ciprofloxacin. The NPs induce faster electron transfer kinetics at its active site, which interferes with the activity of NorA and helps to restore the action of ciprofloxacin. Another mode of action involves the hindrance of the functioning of the membrane protein Omf, which is linked to the penetration of quinolones in the cell membrane. Hence, ZnONPs enhanced ciprofloxacin absorption into the cell (87).

Iram *et al.* proposed ZnONPs as strong metallic NPs that effectively decreased the MIC when combined with the antibiotics against vancomycin-resistant enterococci (VRE) strains. The anti-enterococcal activity of ciprofloxacin, erythromycin, methicillin, and vancomycin has been improved by combination with ZnONPs (88). Fakhar *et al.* reported that the morphology of the ZnO nanostructures may affect the loss in cancerous cells using melanoma and foreskin fibroblast as an experimental model (89,90). The investigation concluded that cell killing factors mainly expressed were: (a) photochemical reactions, (b) nanomaterial morphology, and (c) cell types and nature of resistance. Figure 3 represents zinc oxide nanorods (ZnO NRs) morphology in magnified form giving the concept of basic analogy of materials related to toxicity. Many researchers hold the opinion that ZnO nanomaterials (NMs) can be used as drug delivery vehicles owing to their biocompatibility and low-toxic nature. However, an overdose can produce cell necrosis and certain morphologies of ZnONMs can result in cell toxicity. Different cells have different characteristics of loss in cell viability: some are less resistant and can be easily necrosed, but a few have very high resistance and are resistant to death even at higher doses of drug or radiation (91,92). After a careful investigation of the toxicity of ZnO nanowires (NWs) grown in a femtotip capillary, it was found that significant ROS production was observed, whereas ZnONWs grown in a complex with PpIX were inserted into a foreskin fibroblast cell model after illumination with a UV laser (10 J/cm^2 to 20 J/cm^2 was selected as threshold value). Further details of the mitochondrial membrane potential loss are presented in Figure 4 (90-92).

3.5. TiO_2NPs

TiO_2 is another metal oxide that has been widely studied for its antimicrobial activities (93). Similar to Au, they stimulate a burst of ROS, which injure the membrane, DNA, and various other macromolecules

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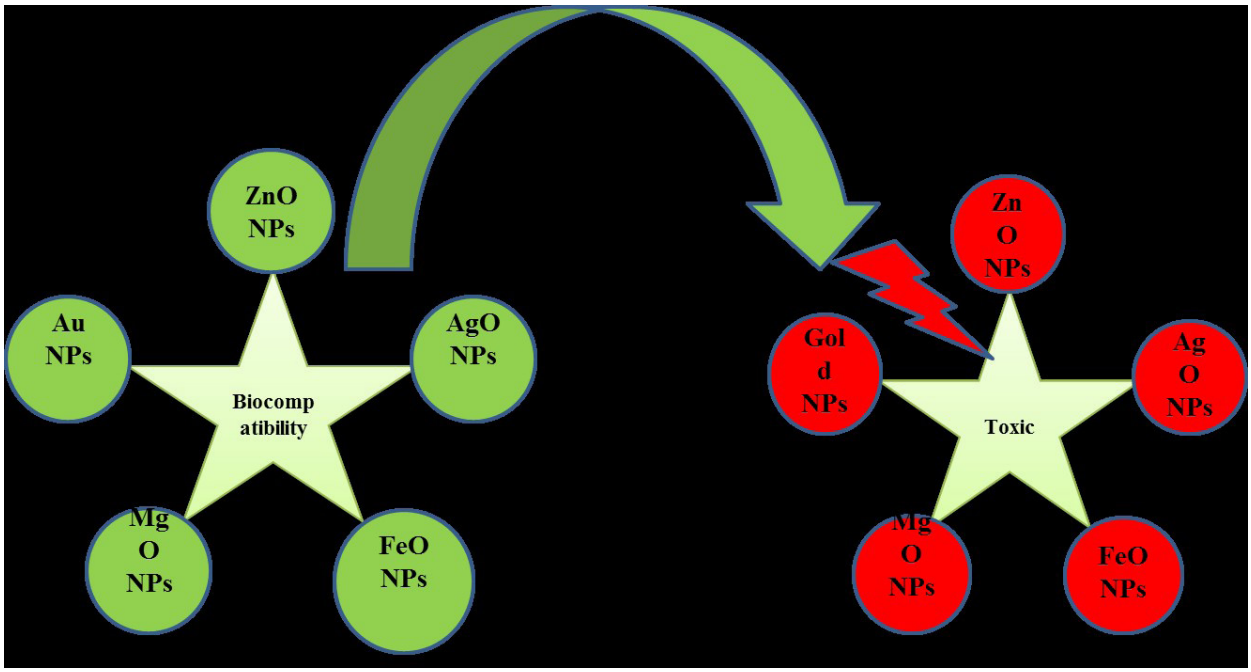

Figure 5. Schematic of a brief research procedure of various metal oxide NPs before and after light exposure.

and functions of the bacterial cell (94). Nano-TiO_2 is considered a strong and effective bactericidal agent with proven efficacy against numerous bacteria, including spores of *Bacillus*, methicillin-resistant *S. aureus* (MRSA), *Streptococcus mutans*, *E. coli*, and *P. aeruginosa* (95-100).

The synergistic effect of TiO_2NPs on the antibacterial activity of various antibiotics has been observed against methicillin-resistant *S. aureus* (MRSA). Roy *et al.* used sub-inhibitory concentrations of TiO_2NPs (20 µg/disc) and observed enhanced antibacterial activity against MRSA with an increase in the inhibitory zone of between 2 mm and 10 mm for penicillin G and 10 mm for amikacin, but in the case of clarithromycin, TiO_2NPs produced a 2-mm enhancement in the inhibitory zone against MRSA. (101). TiO_2NPs enhanced the antimicrobial action of beta lactams, aminoglycosides, cephalosporins, glycopeptides, macrolides, lincosamides, and tetracycline. TiO_2NPs may interact with efflux pumps responsible for the resistance to many clinically significant antibiotics, including fluoroquinolones, which makes these combinations potent for the maintenance and improvement of the activity of fluoroquinolones and other antibiotics and for the reduction of their noxious effects (3).

3.6. Iron oxide NPs (Fe_2O_3NPs)

Among all metallic NPs, Fe_2O_3NPs have attracted particular interest because of the diversity of their scientific and technological applications, which include biosensor antimicrobial activity, magnetic field induced thermal therapy, food preservation, magnetic resonance imaging (MRI), and various systems such as NP-loaded liposomes (102-107).

The antibacterial activities of Fe_2O_3NPs against Gram-positive and Gram-negative bacteria such as methicillin-resistant *S. aureus* (MRSA), *S. pneumoniae*, *Proteus mirabilis*, *Enterobacter aerogenes, B. subtilis, S. aureus, P. aeruginosa, E. coli, K. pneumoniae*, and *Serratia marcescens* have been reported (108-110). The possible mechanism for antibacterial properties is thought to be production of ROS, as described in *S. aureus* by Keenan and Sedlak (111).

Kooti *et al.* investigated the synergistic effect of a $CoFe_2O_4/SiO_2$/Ag composite in conjugation with streptomycin against Gram-positive bacteria (*S. aureus* and *B. subtilis*) and Gram-negative bacteria (*E. coli* and *P. aeruginosa*). The $CoFe_2O_4/SiO_2$/Ag composite incorporated different concentrations of streptomycin (10, 40, 80 mg/mL). The maximum inhibition zones observed for *B. subtilis* were 19 mm at 10 mg/mL streptomycin; at 40 and 80 mg/mL, inhibition zones of 21 mm and 32 mm, respectively, were found for *B. subtilis*. In case of *E. coli*, 19 mm and 22 mm inhibition zones were recorded at 40 and 80 mg/mL, respectively. Lower inhibition was observed for Gram-negative bacteria, but the difference was not too significant to Gram-positive bacteria (112).

The synergistic effects of Fe_3O_4 NPs with the common antibiotics kanamycin and rifampicin were determined against *S. aureus, B. cereus*, *Listeria monocytogenes, E. coli*, and *S. typhimurium*. The results revealed that a mixture of 25 µg Fe_3O_4

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NPs and 5 µg kanamycin resulted in inhibition of all pathogens; in contrast, neither kanamycin nor Fe_3O_4NPs alone exhibited any antibacterial activity. In case of the combination of rifampicin and Fe_3O_4NPs, antibacterial activity against *S. aureus* only was observed, with an inhibition zone of 20.9.0 mm (113). After a thorough review of our own and relevant literature, we concluded that many metal oxides are biosafe and biocompatible prior to light irradiation and can be used as drug delivery vehicles, but after suitable/matchable wavelength of light irradiation, many become toxic and are very useful for cancer therapies, as shown in Figure 5.

3.7. Gadolinium-doped Fe_2O_3NPs (Gd+Fe_2O_3NPs)

Cancer detection and treatment using appropriate medical techniques are the major challenges of the modern age. Physicians and oncologists can significantly improve a patient's survival rate and quality of life with early detection and proper staging.

Biopsy, optical medical imaging techniques e.g., Optical Coherence Tomography including nonlinear microscopy, and confocal microscopy have been practiced in many cancer hospitals and research centers for the past few decades, but the nanotechnology revolution has greatly impacted on human life as it has an enormous potential to change the world, especially in the fields of health and medical science, including the development of novel sophisticated probes, biosensors, significant drug delivery, and the recognition of cancer diagnosis applications. The current projects are focused on the production of remarkable and significant changes, especially in the health and medical sectors, which play important roles in the bioavailability of drug and two photon deep dynamic therapies.

Nanotechnology has been played a dynamic role in the development of science and technology, especially in clinical and biomedical/oncological fields. However, despite the major development in clinical and biomedical applications, there are unfortunately still many imperfections and in cancer treatments. Scientists are focusing on the development of smart individual and hybrid/doped forms of nanomaterials and quantum dots with diverse functional groups for multipurpose treatment modality since last three decades. Many were used for cancer diagnostics and treatment after the introduction of various novel techniques, such as photothermal and photodynamic therapies. Further advancements in this field are a prerequisite of the modern era (114-119).

Gd is a paramagnetic metal ion, which is extensively used in MRI, especially when encapsulated with a chelating agent. In addition, Gd offers great potential as an MRI material. Gd-based contrast agents for the MRI of brain have been used in the last three decades owing to the unique diagnostic and treatment properties, which include the enhancement of the magnetic properties of nearby water molecules in targeted areas. In addition, Gd is very popular candidate owing to the following characteristics: improvement of the visibility of specific organs, blood vessels, and tissues, which must be helpful for biomedical applications. Gd might be toxic in specific circumstances, such as when it is bound or encapsulated with some chelating agent responsible for the biodistribution of Gd towards specific targeted sites. Oncologists and physicians have reported the excellence of Gd-based contrast agents for MRI for patient cancer imaging and treatment worldwide. From the literature survey, we determined that dynamic Gd enhancement for MRI purposes was more suitable for acute group retroperitoneal fibrosis compared with chronic group fibrosis. The difference was very significant for acute (mean, 1.8.6; range, 1.8.0–1.9.5) and chronic (mean, 1.3.7; range, 1.2.6–1.6.1). Gd-based contrast agents (GBCAs) have been approved by the FDA for the use of better and improved form of body organs and tissue information associated with MRI. Gd agents are radiodense and can be used for opacification in CT and angiographic examinations instead of iodinated radiographic contrast media. However, nephrotoxic effects within range of same doses are still debatable (120-123). The ideal size for Gd contrast agents in blood circulation has been reported as 7–12 nm, which is also the case for neutron capture therapy combined with radio immunotherapy. Several hydrophobic contrast agents with additional antibodies and dendrimer cores localize into the liver very quickly; although hydrophilic contrast agents operate differently their mode of accumulation is highly suited for lymphatic imaging.

Despite vast progress in the fields of clinical practice and MRI, there are still many flaws and a need for a comprehensive and reliable non-destructive technique for the identification of inner body organs. Glycosaminoglycan concentration (GAG) of human cartilage plays an important role in many biomedical applications, such as knee and hip replacement surgery. Recently reported data demonstrated that the GAG distribution was correlated with charged contrast agent gadolinium diethylene triamine pentaacetic acid $(Gd(DTPA))^{2-}$, which both have an inverse relationship of the biodistribution in human cartilage (124-127). A schematic layout of future applications is shown in Figure 6.

3.8. Copper NPs (CuNPs/CuONPs)

Cu is a semiconducting metal with a monoclinic structure. It is available in the form of copper oxide (CuO)/copper (II) oxide/cupric oxide. Among these, CuO has achieved particular importance, as it is the most simple, and presents a wide range of physically reliable features, such as electron correlation effects,

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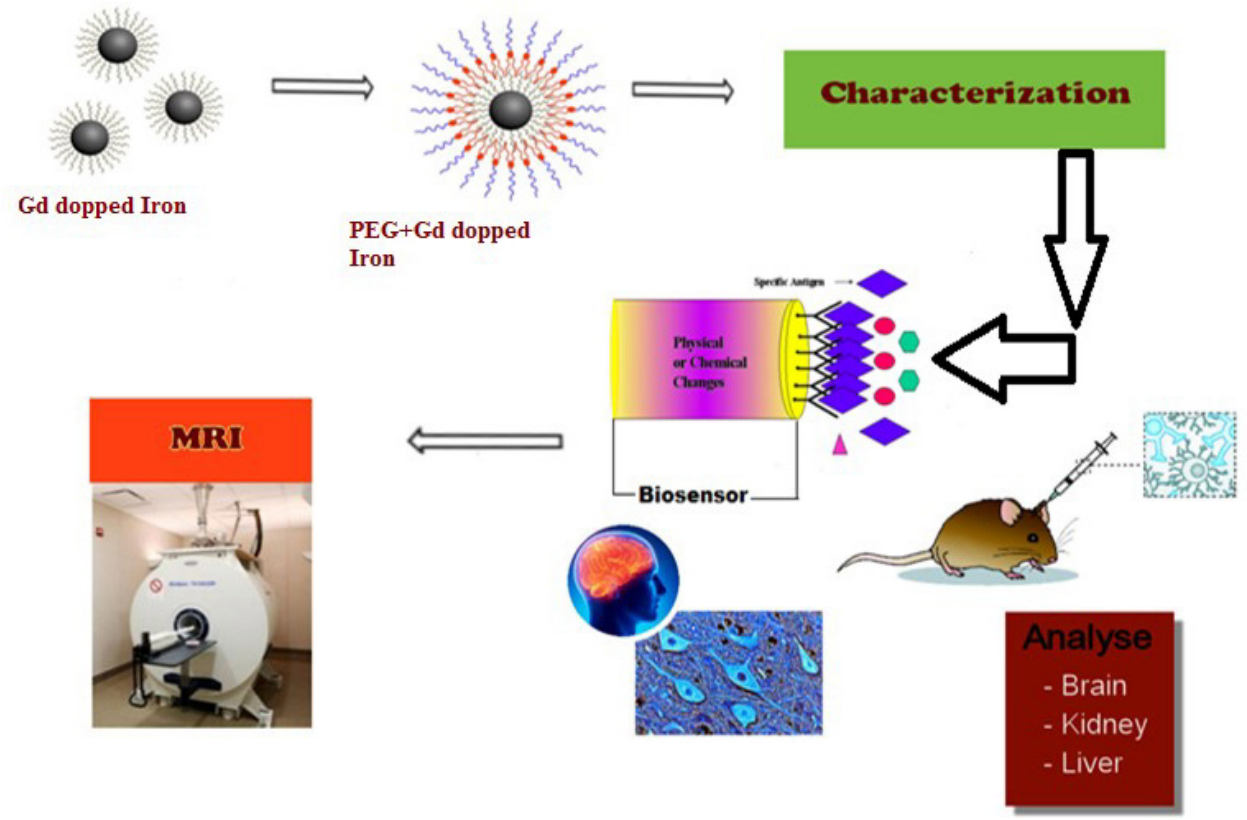

Figure 6. Schematic diagram of gadolinium-doped iron oxide nanoparticles for PDT, MRI, and biosensing applications.

spin dynamics, and high temperature superconductivity (128-129). Cu has been reported as an antibacterial and antifungal agent (a fungicide) and has been used in coatings, dietary supplements, nanowires, and nanofibers (130). Meanwhile, Ag and Cu ions have been recommended to disinfect hospital-generated wastewater (131). However, CuNPs have exhibited stronger bactericidal activities as compared with Cu ions. The bactericidal potential of CuNPs has been reported against *E. coli, K. pneumoniae, Bacillus megaterium, S. aureus* and *S. typhimurium* (132-135). Moreover, the potential of CuNPs against biofilm-producing *P. aeruginosa* has also been reported (136). CuNPs were found to exert toxic effects, including the generation of ROS, damage to mitochondria, lipid peroxidation, and DNA damage (137, 138).

Only a few studies have reported the synergistic effects of CuNPs conjugated with antibiotics. The synergistic effect of amoxicillin with CuONPs was reported against *E. coli* and *S. aureus*. The inhibitory effects of CuONPs were enhanced by almost 9.9.% against *E. coli* and 8.9.% against *S. aureus* when used together with amoxicillin compared with the inhibitory effect of CuONPs and amoxicillin individually (139).

Another study by Khurana *et al.* reported the synergistic effect of CuNPs with tetracycline and kanamycin against *B. subtilis* and *P. fluoresence*. In the case of kanamycin, antibacterial activity was increased by up to 3% against *B. subtilis* and up to 20% against *P. fluorescence* at 250 ppm CuNPs. However, at 100 ppm, the biocidal activity for tetracycline was increased by up to 30% against *B. subtilis*, but in the case of *P. fluoresence* no synergistic effect between CuNPs and tetracycline was observed. In the case of the CuNPs-kanamycin conjugate, increases of 16% and 3% in inhibition zones for *B. subtilis* and *P. fluoresence*, respectively, were observed (37)).

3.9. MgONPs/CaONPs

MgO and CaONPs exert strong bactericidal activity owing to the alkalinity and generation of reactive oxygen species. It has been reported that MgO and CaONPs are responsible for the generation of superoxide ions and also raises the pH through the hydration of MgO and CaO with water (140). MgONPs act as efficient bactericidal agents against Gram-positive bacteria as well as Gram-negative bacteria (141). Jeong *et al.* reported the antibacterial effect of $CaCO_3$ NPs against Gram-negative and Gram-positive bacteria, such as *E. coli*, *S. typhimurium*, *S. aureus*, and *B. subtilis*. It was observed that $CaCO_3$ was converted to CaO during heat treatment and the CaONPs exhibited significant activity against test organisms (142).

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Iram *et al.* reported enhancement of the anti-enterococcal activity of different antibiotics when combined with metal oxide NPs such as those of ZnO, MgO, and CaO. It was observed that the MICs of ciprofloxacin, erythromycin, and vancomycin were significantly reduced to 4–512 µg/mL when combined with 10 mM CaO and MgONPs (88).

3.10. Toxicity caused by NPs

We have previously discussed the beneficial impact of NPs in combination with antibiotics on human health. However, the adverse effects caused by certain NPs should not be ignored. Given the extraordinary use of NPs in the medical field, concerns about access to human organs and toxicity of NPs have been raised. NPs can be toxic at certain concentrations and their correct use is necessary to avoid various health problems. Not only the dose, but also the route of NP entry to the human body, is a major issue that is independent of dose concentration. A strong relationship exists between the route of administration and NP toxicity, as accumulation and distribution will differ (143).

NPs may reach the body by inhalation, oral ingestion, skin contact, and intravascular injection (144). After ingestion, NPs can be distributed to different body organs. Depending on the mode of administration and the target organs, recent toxicological studies have proposed inflammation and oxidative stress as the underlying mechanisms of nano-cytotoxicity (145).

One of the major issues in the investigation of nano-cytotoxicity is the standardization of the experimental conditions. To overcome this problem, Khlebtsov *et al.* (146) proposed to standardize the methods for nontoxicity assessment to establish the relationships among mode of administration, particle size and shape, and cells and organs studied. Moreover, a clear relationship between the *in vitro* and *in vivo* studies should be established, as limited number of *in vivo* human studies is available. Although some *in vitro* studies have suggested that NPs have the ability to induce toxicity in humans, but as *in vivo* conditions are quite different, more studies should be performed in order to establish a clear relationship between the *in vivo* and *in vitro* effects of nanotoxicity (147-149).

4. CONCLUSIONS AND FUTURE PERSPECTIVES

4.1. Conclusions

NPs serve as nano-weapons to combat the bacterial resistance to conventional antibiotics. Indeed, metal and metal oxide NPs have demonstrated promising antibacterial actions against multidrug-resistant Gram-positive and Gram-negative bacteria. However, when they are used in combination with antibiotics, they not only enhance the delivery of drug to the site of action, but also increase the antimicrobial action of antibiotics and decrease the side effects related to the extensive use of broad-spectrum antibiotics. All of the metal and metal oxide NPs discussed above exhibited potential synergistic activities with various antibiotics. The synergistic effects of NPs and antibiotics suggest that it is one of the most promising ways to cope with the increased threat of antibiotic resistance. There are several metallic NPs, such as zirconium oxide, CaO, and MgONPs, which exhibited promising bactericidal activities; however, their synergistic effect with standard antibiotics has not yet been fully investigated. Therefore, studies should be conducted to determine their role as an adjuvant when combined with routinely used antibiotics. Antibiotics used in combination with NPs could restore the activity of previously used antibiotics, such as penicillin, to which bacteria have acquired resistance. Some studies have uncovered the possible mechanisms for synergy, but there is a need for additional investigation to determine the exact mode of action. In addition, studies should be performed on the combination of NPs with other antimicrobial agents, such as plant essential oils and disinfectants, so that more alternative formulations could be investigated against resistant bacterial strains.

Antibiotic delivery using nanomaterials offers many advantages: 1) controllable and relatively uniform distribution in the target tissue; 2) improved solubility; 3) sustained and controlled release; 4) improved patient compliance; 5) minimized side effects; and 6) enhanced cellular internalization (56–58).

4.2. Future perspectives

Metal NPs are unique moieties that exhibit many functional and structural properties to enable the construction of nanomaterials for antimicrobial therapy. The potentiated antimicrobial activity of nanoantibiotics offers an excellent chance for the substitution of traditional antibiotics. For the development of more potent nanoantibiotics, a detailed knowledge of cellular uptake phenomena is of utmost significance. So far, no FDA approved product has been made available for systemic human usage; hence, future research should be directed to elucidate the physicochemical, biological, and pharmacotoxicological attributes of nanoantibiotics in order to develop safe and admissible products. Although this appears a challenging task, the combination of metal NPs and antibiotics with sequential multistage targeting against drug-resistant bacterial planktons might be an efficient therapeutic option in the near future to combat antimicrobial resistance and prove a game changer in the field of nanomedicine. In conclusion, the realm of nanoantibiotics will serve

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as next-generation therapeutics to mitigate the threat of superbugs. Cutting-edge research, committed efforts, a vast number of applications, and the commercialization of nanoantibiotics will indeed result in improved quality of life.

4.3. Summary

- The extensive use of antibiotics has resulted in the development of multidrug-resistant bacteria that are ultimately pushing the human race back to the pre-antibiotic era.
- Metal and metal oxide NPs offer promising antimicrobial activity against various bacterial pathogens.
- NPs, which can be used as a carrier, assist in the controlled and uniform drug delivery to the targeted sites.
- The combination of antibiotics and NPs exhibits synergistic effects.
- Transition metal NPs are extensively studied; however, NPs of other metals such as alkaline earth metals are yet to be explored.
- The exact bactericidal mechanism of NPs is still undefined.

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Send correspondence to: Sumreen Hayat, Department of Microbiology, Government College University, Allama Iqbal road, 38000, Faisalabad, Pakistan Tel: 92-333-6178428, E-mail: sumreenhayat@gcuf.edu.pk

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