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Synergism Effect of Antibiotics and Silver Nanoparticles to Control Antibiotic Resistant Bacteria: A Mini Review

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ABSTRACT
Antimicrobial resistance (AMR) is a serious threat to global public health. It causes the prevention and treatment of infectious diseases become more difficult, costly, and sometimes require toxic alternatives. One of the strategies to address this crisis is by developing new drugs formulation using nanoparticles (NPs). AgNPs widely known for its antibacterial activity and the synergism of AgNPs with antibiotic compound is reported to enhance its activity. Additionally, its activity is against the resistant bacteria. This review informs the advancement in AgNPs development and highlight the AgNPs antibacterial mechanism of action, and the synergistic effects of AgNPs-antibiotics.

Keywords: *Antimicrobial, S silver nanoparticle, Antibiotic resistance.*

1. INTRODUCTION

WHO professed antimicrobial resistance (AMR) as one of the top 10 threats impacting global public health and development [1]. Infection caused by resistance bacteria, fungi, parasites, and virus are getting difficult to treat and raising the chance of transmission, disease severity, longer hospitalization, and death [1,2]. The United Nation also accentuates AMR as a risk that should be overcome, since it can hamper the attainment of Sustainable Development Goals (SDGs) [2–4].

Several approaches had been proposed to protract the emergence and relegate the transmission of resistant microorganism, one of them is by the development of drugs formulation using nanoparticles (NPs) strategy [5–7]. Silver nanoparticles (AgNPs) has been increasingly utilized to combat drug resistance microbe [6–9]. The ability of NPs to penetrate cell membrane and disturb molecular pathways of pathogenic microorganism, in addition to their ability to avoid common resistant mechanisms, were the key point of its utilization for development for antimicrobial drugs [6]. Synergism effect of NPs and antibiotics drug is reportedly effective to enhance the antibiotics effect, inhibit biofilm formation, quorum sensing obstruction, feasibly plasmid curing, and tackle resistance microbe [6,10]. Therefore, better understanding on AgNPs as bactericidal agent and the enhancement of its activity through the combination of antimicrobial agent and the nanoparticles is indeed salient.

Although, there were several reviews on the production, characterization, and antibacterial activities of AgNPs, reports about the mechanism of action of AgNPs is still very limited, even more for the synergism effect of AgNPs-antibiotics. Therefore, this review summarizes the recent development of AgNPs focusing on the AgNPs antibacterial mechanism of action, and the synergistic effects of AgNPs-antibiotics.

2. AgNPs PHYSICOCHEMICAL CHARACTERISTICS AFFECTING ANTIBACTERIAL ACTIVITY

The AgNPs physicochemical parameters that is known to be affecting its antimicrobial activity are size, shape, surface charge, concentration, and colloidal state [8,11]. Smaller size AgNPs has better stability, biocompatibility, and antimicrobial activity [12,13]. Generally, nanoparticles of size $\leqslant$ 50 nm seem to have better activity [8] while particles sized between 1 – 12 nm are capable to infiltrate the bacterial cell wall [14]. Dong et al. [13] reported that smaller AgNPs had lower minimum inhibitory concentration (MIC) and minimum bactericidal concentrations (MBC) against Vibrio

natriegens, which indicate better antibacterial activity (10±5 nm > 30±5 nm > 60±5 nm > 90±5 nm). Better activity of smaller particle size was caused by its larger surface-area-to-volume ratio which rises the contact area with target organisms and its penetrability that makes it possible to reach the nuclear content of the bacteria [15–17]. The smaller particle size also shows more noticeable attachment with the cell membranes, which further resulting in risen membrane permeability, cell damage and death [15].

The morphology of AgNPs can be spherical, disk, pentagonal, cuboidal, hexagonal, irregular, polygonal, round-triangle, triangular, rod-shaped, nanocubes, nanospheres, or nanowires [18,19]. The shape of AgNPs is one of important factors that effects bacterial toxicity, as it might influence the ability of AgNPs to dissolve in liquids and release Ag+ ions, the cellular uptake mechanism, and the plasmonic properties [11,17,20,21]. Hong et al. [19] compared the bactericidal activity of nanocubes, nanospheres, and nanowires AgNPs and it was reported that the MIC of each samples against E. coli were 37.5, 75, and 100 μg/mL, respectively. Silver nanowires had the weakest antibacterial activity due to its smaller effective specific contact areas with bacteria compared to silver nanocubes and silver nanospheres. Furthermore, the facets reactivity also plays role in the bactericidal activity of the AgNPs. Nanocubes with {100} facets are able to locate bacterial cell membranes faster and induce cell membrane damage easier compared to nanospheres with {111} facets. Acharya et al. [21] reported that spherical and rod-shape AgNPs had excellent antibacterial activity against Gram-negative (P. aeruginosa AL2-14B, K. pneumoniae AWD5, and E. coli ATCC 25922) and Gram-positive bacteria (B. subtilis AST5-2 and S. aureus ATCC 25923). The spherical shape particle with larger surface area showed lower MIC value compared to that of the rod-shape particle. Pal et al. [22] also verified a shape-dependent association where truncated triangular-shaped AgNP had greater bactericidal activity against E.coli compare to that of spherical and rod shaped AgNPs. On the hand, Actis et al. [23] found that the shape of AgNPs (spherical, triangular and cuboid) did not have biocidal effect on Staphylococcus aureus susceptibility.

The synthesis method of AgNPs could affect particles surface charges. It was reported that the negatively charge AgNPs could be synthesized through the silver nitrate reduction process using sodium borohydride. While neutral particle was produced when rice starch was used as reducing agent. Meanwhile positively charge AgNPs was formed when the synthesized process conducted using sodium borohydride as reducing agent and the particles capped with 1-dodecyl-3-methylimidazolium chloride [16,24]. The positively charged AgNPs had the highest bactericidal activity, followed by the neutral and the negatively charged particles. It was identified that bacteria had negatively charge membrane structure, due to the presence of carboxyl, phosphate, and amino groups, and protein with sulfur- and phosphorus-ion. Although the neutrally charged particles had intermediate activity, they were effective against most bacterial species tested [16].

The concentration of AgNPs plays role at microbial toxicity. AgNPs sized about 10 nm was able to inhibit B. subtilis growth for 12 h at concentrations of > 5 ppm, while the lethal doses were observed at ⩾ 10 ppm. It was also reported that AgNPs impede the growth of B. subtilis and its entry to the exponential phase [11]. Other studies also proved that the increasing concentration of AgNPs correlate with better antibacterial activity against E. coli (DH5α) and MDR E. coli (DH5α-MDR) [25], S. aureus, S. infantis, S. dysenteriae, V. parahaemolyticus, [26], P. aeruginosa, and S. sciuri [27].

Colloidal form (nanosized suspension) of AgNPs demonstrated improved antimicrobial ability over AgNPs in liquid system [26,28,29]. Colloidal silver possed enhanced bactericidal potential because it could catalyze and destabilize the bacterial enzymes required for the utilization of oxygen. It also altered the profile of phosphotyrosine in the bacterial proteins that lead to the modulation of signal transduction pathways and bacteria growth inhibition [8,30].

3. ANTIBACTERIAL MECHANISM OF AgNP

The propose route of AgNPs antibacterial action is through direct contact with the bacteria cell surface and membrane [31–33], penetration through bacteria cell which causes intracellular cell damage, cell toxicity and oxidative stress, and signal transduction pathways alteration [8,33]. The positive surface charge of AgNPs has a vital role to the adhesion of the particles to negatively charge bacterial cell membrane [16]. The interaction of the AgNPs and target microorganism affects the bacteria cell regulation, membrane penetration, and interfere molecular pathways [6,34]. AgNPs can attach onto bacterial cell wall then subsequently penetrates and perforates the cell membrane which lead to bacterial cell death [25].

AgNPs leach bioactive Ag+ ions in aerobic condition [11]. The release rate of the ions from the nanoparticulate is reliant on particulate size, surface morphology, porosity, environmental O2 concentration, desorption of chemisorbed ions from the particulate surface, and oxidative dissolution of Ag+ in the aqueous environment. Xiu et al. reported that Ag+ is accountable for the antibacterial activity [35]. These ions cause microbial cell wall rupture, protein denaturation, respiratory blockage, and even inducing cell death [11,33]. Additionally, they affect the adherence, structure, and porosity of the extracellular polymer of bacterial biofilm [33]. Ag+ ions which enter B. subtilis cells wield toxic

impacts and intracellularly oxidized to Ag2O [11]. The interaction of Ag+ and negatively charged compounds i.e., phosphate, carboxyl, and amino groups, in the bacterial cell wall causes Ag aggregation [36] and cell wall destabilization which can be observed through the physical separation of bacteria cell wall and cytoplasmic membrane [37]. The neutralization of the cell membrane surface charge also affects membrane cell integrity and increasing its permeability. The AgNPs treated cell of E. coli and P. aeruginosa has membrane leakage. It was observed through microscopic imaging that the intracellular components were pooling around the bacteria cells. In addition, stress conditions lead to the arresting of cell division and cell elongation [14]. The exposure of AgNPs which caused cell wall rupture, eventually creates an electrostatic imbalance, fall down of the proton force, and intracellular K+ leakage [13,14].

Both AgNPs and Ag+ are responsible for the formation of ROS, with AgNPs reportedly form more ROS compared to its ionic state [14,38]. AgNPs triggered the over production of ROS and free radicals, including superoxide anions (O2-), hypochlorous acid (HOCl), singlet oxygen, hydrogen peroxide (H2O2), and hydroxyl radicals (OH*) [8,14,39], which lead to the oxidation of macromolecular substances like protein and nucleic acids, and subsequently inhibit cell proliferative [13,25,40,41]. Ag+ interfered with the normal function of the bacterial electron transports chain of E. coli, thereby facilitating the formation of ROS [42]. Ag+ also frees radicals which will increase the cell membrane porosity, which lead to cell damages and eventually cell death [14,25].

AgNPs treatment could lower reductase activity and reduce protein expression [11]. It was observed that AgNPs at concentration of 25 ppm or above could significantly decrease reductase activity and increase membrane permeability in B. subtilis. Furthermore, it negatively affects the expression of Phag-GFP and cytosolic protein.

The MIC of AgNPs against clinical isolates of multidrug-resistant (MDR)- and extensively drug-resistant (XDR)-M. tuberculosis were 4 and 1 µg/mL 1 µg/mL, respectively [31]. While other studies reported that AgNPs had MIC of 6.25 to 12.5 µg/mL against the MDR- and XDR-M. tuberculosis when evaluated using Microplate Alamar Blue Assay (MABA) method [43]. Heidary [31] reported that the antibacterial activity of AgNPs were through contact killing and ion-mediated killing. It was also presumed that M. tuberculosis strains sometimes go to latent phase and survive after AgNPs treatment, thus it needs to be combined with anti-TB drugs.

Bioactive ion Ag+ and ROS lead to the disruption of the metabolic pathways and DNA degradation [11,25,33,41]. The damage of DNA strand, DNA base-pairs modifications and deoxyribose fragmentation in bacterial cells occur due to the formation of Ag+-complex with double and triple hydrogen bonds in DNA base pairs [41]. Hsueh et al. [11] reported that AgNPs at the concentration of 10 ppm or greater were able to compromise the chromosomal DNA integrity and morphological changes in the B. subtilis cell.

4. SYNERGISTIC EFFECTS OF AgNPs WITH ANTIBIOTICS

AgNPs could improve the inhibitory effects of antibiotics. Several studies reported the synergism effect of AgNPs and antibiotic are listed in Table 1. Mazur et al. [40] reported that the combination of AgNPs and gentamicin showed synergistic effect (Fractional Inhibitory Concentration or FIC $\leqslant$ 0.5) which resulted in lower MIC value against all clinical strains of S. epidermidis that was resistant to beta-lactam antibiotics (MRSE) and macrolides, lincosamides, and streptogramins (MLSB). While AgNPs alone at a concentration of 1400 µg/mL did not exhibit antibacterial activity.

Khatoon et al. [9] synthesized Amp-AgNPs through the reduction of Ag+ ions using ampicillin. The product yield was found to be optimum when the concentration of silver nitrate and ampicillin were 10 mM each and the synthesis temperature was 60 °C. The 90% inhibition of Amp-AgNPs against ampicillin resistant E. coli and S. aureus were 10 and 3 µg/ml, respectively. Additionally, Amp-AgNps susceptibility against multidrug resistant bacteria P. aeruginosa and K. pneumonia was found to be 20 and 28.12 µg/ml, respectively. Compare to ampicillin and AgNPs which had MIC90 range between 125-720 and 300-640 µg/ml, respectively, these results showed that antibiotic adsorbed AgNPs enhanced bactericidal activity. The mechanism of action of Amp-AgNPs was through Amp-AgNps penetration to bacteria cell which then damaged the DNA and led to cell death. It was also found that it caused cell destruction and cellular propagation inhibition.

Other study reported the synergism effect of tetracycline (TC) and AgNPs [44]. TC-AgNPs yield was optimal when synthesized using the combination of silver nitrate, tetracycline, and sodium hydroxide at molar ratio of 1:6:24. Here, tetracycline works as co-reducing and stabilizing agent. The reaction was conducted in the dark room for 15 minutes. The average size of TC-AgNPs was 15±5 nm and the colloidal solution was stable for several weeks. These particles were active against tetracycline resistant E. coli ST648 and S. aureus ST398 with MIC of 40 and 62.3 µg/ml, respectively.

The synergistic effect of antibiotic and AgNPs was also reported by Thomas et al. [45]. It was reported that the incorporation of antibiotic and AgNPs showed remarkable antibacterial activity against all multidrug resistant strain of S. epidermidis. Esmaeillou et al. [46]

successfully incorporated vancomycin to thioglycolic acid-stabilized AgNPs and these particles showed antibacterial activities with MIC of 0.1 µg/ml for vancomycin resistant Enterococcus faecalis and MIC ⩽ 0.02 µg/ml for methicillin-resistant Staphylococcus epidermidis. In accordance with other studies, incorporation of AgNPs to antibiotic i.e., cefotaxime, ceftazidime, meropenem, ciprofloxacin, or gentamicin, greatly boosted antibacterial activity against multiresistant β-lactamase and carbapenemase-producing Enterobacteriaceae [47]. These presumably because the incorporation of antibiotic and AgNPs could damage the bacteria cell wall, affect membrane cell permeability, disturb bacterial metabolic processes, inhibit the production of enzymes responsible for resistance, and/or inhibit the hydrolysis process of antibiotic.

McShan et al. [48] reported that AgNPs could be conjugated with various antibiotic class such as tetracycline (polykeptide), neomycin (aminoglycoside), and penicillin (β-lactam). These conjugates showed dose-dependent inhibition against Salmonella typhimurium DT104 growth with IC50 0.07 µg/mL and 0.43 µg/mL for tetracycline-AgNPs and neomycin-AgNPs, respectively. Unfortunately, the penicillin conjugated AgNPs was not susceptible to the bacteria. It was because the tetracycline- or neomycin-AgNPs conjugates could efficiently inhibit the bacteria growth through the improved binding capacity of tetracycline- or neomycin-AgNPs conjugate with bacterial, but not by penicillin-AgNPs.

Table 1. Synergistic effect of AgNPs and antibiotic

Antibiotic	Target Bacteria	Antibiotic Resistance Type	Antibacterial Activitya	Mechanism Of Action	Ref
Gentamicin	*S. epidermidis*	Gentamicin-resistant	MIC = 0.97-62.5 µg/ml	Generation of ROS	[40]
Ampicillin	*E. coli*	Ampicillin resistant	MIC_{90} = 10 µg/ml	DNA damage, cell destruction and inhibition of cellular propagation.	[9]
	S. aureaus	Ampicillin resistant	MIC_{90} = 3 µg/ml		
	P. aeruginosa	Resistant to cephalosporins, aminoglycosides, carbapenems and ß-lactamase inhibitors	MIC_{90} = 20 µg/ml		
	K. pneumonia	Resistant to cephalosporins, aminoglycosides, carbapenems and ß-lactamase inhibitors	MIC_{90} =28.12 µg/ml		
Vancomycin	*E. faecalis*	Vancomycin resistant	MIC = 0.1 µg/ml	N.a.	[46]
	S. epidermidis	Methicillin resistant	MIC = ≤0.02 µg/ml		
Tetracycline	*E. coli* ST648	Tetracycline resistant	MIC = 40 µg/ml	N.a.	[44]
	S. aureus ST398	Tetracycline resistant	MIC = 62.3 µg/ml		
Cefotaxime	*E. coli*	Beta-lactam resistant	MIC = 0.03 µg/ml	Damage the cell wall, influence membrane cell permeability, affect bacterial metabolic processes, inhibit production of enzymes responsible for bacterial multidrug resistance, or inhibit the enzymatic process of antibiotic hydrolysis.	[47]
Ceftazidime			MIC = 0.125 µg/ml		
Meropenem			MIC = 0.06 µg/ml		
Ciprofloxacin			MIC = 0.125 µg/ml		
Gentamicin			MIC = 0.125 µg/ml		
Cefotaxime	*K. pneumoniae*	Beta-lactam resistant	MIC = 1 µg/ml		
Ceftazidime			MIC = 2 µg/ml		
Meropenem			MIC = 0.06 µg/ml		
Ciprofloxacin			MIC = 0.2 µg/ml		
Gentamicin			MIC = 16 µg/ml		
Cefotaxime	*E. coli*	Ampicillin resistant	MIC = 1 µg/ml		
Ceftazidime			MIC = 2 µg/ml		
Meropenem			MIC = 0.06 µg/ml		
Ciprofloxacin			MIC = 8 µg/ml		
Gentamicin			MIC = 0.125 µg/ml		
Cefotaxime	*K. pneumoniae*	Carbapenemase resistant	MIC = >16 µg/ml		
Ceftazidime			MIC =2 µg/ml		
Meropenem			MIC = 4 µg/ml		
Ciprofloxacin			MIC = 8 µg/ml		
Gentamicin			MIC = 0.125 µg/ml		
Tetracycline		Multidrug-resistant	IC_{50} = 0.07 µg/ml		[48]

Antibiotic	Target Bacteria	Antibiotic Resistance Type	Antibacterial Activitya	Mechanism Of Action	Ref
Neomycin	*S. typhimurium* DT104		IC_{50} = 0.43 µg/ml	Bacteria cell growth inhibition and bacterial binding.	
Penicillin			IC_{50} = 0 µg/ml		
Fusidic acid	*S. epidermidis* 73	Multidrug-resistant	ZOI = 25 mm	Bacterial enzymes inhibition, generation of free radicals, damaging bacterial DNA and interfere DNA replication	[45]
Gentamycin			ZOI = 15 mm		
Gentamycin	*S. epidermidis* 145	Multidrug-resistant	ZOI = 10 mm		
Ciprofloxacin			ZOI = 23 mm		
Fusidic acid	*S. epidermidis* 152	Multidrug-resistant	ZOI = 13 mm		
Ciprofloxacin			ZOI = 18 mm		

[a] MIC: minimal inhibitory concentration of antibiotic-AgNPs conjugates at AgNPs concentration of 0.4 µg/ml; ZOI: zone of inhibition.

5. CONCLUSION

The widespread concern about antibiotic resistance microbes promotes research in the discovery of new antibiotic compounds and pharmaceutical development of antibiotic drugs. AgNPs has been proven its antibacterial activity and has been used in various products such as, cosmetics, medical products, and antimicrobial dressings. The article provides state-of-the art review on the physicochemical factors that affect its bactericidal activity and its mechanism of action. It highlights the synergism antibacterial activity of antibiotic-AgNPs conjugates against drug resistance bacteria. Studies reported that AgNPs physicochemical parameters that affects the antimicrobial activity of the particles are size, shape, surface charge, concentration, and its colloidal state. The antibacterial activity of these nanoparticles works through direct contact with the bacteria cell surface and membrane, penetration through bacteria cell that leads to intracellular cell damage, cell toxicity and oxidative stress, and signal transduction pathways alteration. These activities are enhanced when the AgNPs were conjugated with antibiotics. Information regarding the effects of AgNPs at a cellular level is essential to further determine the dosage and safety profile. In addition, knowledge about the characteristic of AgNPs in biological system and in synergism with antibiotic will offer the essential information in the nanomaterials technologies development to prevent and treat infections caused by pathogenic bacteria. That is why suitable approaches for their usage must be premeditated and fostered to relegate the emergence of resistant strains.

AUTHORS' CONTRIBUTIONS

All authors conceived and designed this study. All authors contributed to the process of revising the manuscript, and at the end all authors have approved the final version of this manuscript.

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