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Review

# Antimicrobial activity of the metals and metal oxide nanoparticles

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ABSTRACT

The ever increasing resistance of pathogens towards antibiotics has caused serious health problems in the recent years. It has been shown that by combining modern technologies such as nanotechnology and material science with intrinsic antimicrobial activity of the metals, novel applications for these substances could be identified. According to the reports, metal and metal oxide nanoparticles represent a group of materials which were investigated in respect to their antimicrobial effects. In the present review, we focused on the recent research works concerning antimicrobial activity of metal and metal oxide nanoparticles together with their mechanism of action. Reviewed literature indicated that the particle size was the essential parameter which determined the antimicrobial effectiveness of the metal nanoparticles. Combination therapy with the metal nanoparticles might be one of the possible strategies to overcome the current bacterial resistance to the antibacterial agents. However, further studies should be performed to minimize the toxicity of metal and metal oxide nanoparticles to apply as proper alternatives for antibiotics and disinfectants especially in biomedical applications.


**Contents**



## 1. Introduction

Emergence of the antibiotic resistance pathogens has become a serious health issue and thus, numerous studies have been reported to improve the current antimicrobial therapies. It is known that over 70% of bacterial infections are resistant to one or more of the antibiotics that are generally used to eradicate the infection [1]. Development of new and effective antimicrobial agents seems to be of paramount importance. The antimicrobial activity of metals such as silver (Ag), copper (Cu), gold (Au), titanium (Ti), and zinc (Zn), each having various properties, potencies and spectra of activity, has been known and applied for centuries [2].

Recently, nanotechnology has offered great possibilities in various fields of science and technology. Pharmaceutical nanotechnology with numerous advantages has growingly attracted the attention of many researchers [3]. The application of nanomaterials in the drug delivery systems has been investigated for more than twenty years bringing about innovation of dosage forms with improved therapeutic effects and physicochemical characteristics [4,5]. Several types of nanoparticles

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and their derivatives have received great attention for their potential antimicrobial effects. Metal nanoparticles such as Ag, silver oxide ($Ag_2O$), titanium dioxide ($TiO_2$), silicon (Si), copper oxide (CuO), zinc oxide (ZnO), Au, calcium oxide (CaO) and magnesium oxide (MgO) were identified to exhibit antimicrobial activity. In vitro studies revealed that metal nanoparticles inhibited several microbial species.

The kind of the materials used for preparing the nanoparticles as well as the particle size were two important parameters that affected the resultant antimicrobial effectiveness [6,7]. Generally nanoparticles have different properties compared to the same material with the larger particles owing to the fact that the surface/volume ratio of the nanoparticles increases considerably with decrease in the particle size [8,9]. Indeed, in the nanometer dimensions, fraction of the surface molecule is noticeably increased which in turn improves some properties of the particles e.g. heat treatment, mass transfer, dissolution rate, catalytic activity [8,10].

The exact mechanisms for antibacterial effect of nanometals are still being investigated, but there are two more popular proposed possibilities in this regard: (a), free metal ion toxicity arising from dissolution of the metals from surface of the nanoparticles and (b), oxidative stress via the generation of reactive oxygen species (ROS) on surfaces of the nanoparticles [11].

Furthermore, morphological and physicochemical characteristics of the nanometals have been proven to exert an effect on their antimicrobial activities [6,12]. It is known that the small nanoparticles have the strongest bactericidal effect [8,11,13,14]. The positive surface charge of the metal nanoparticles facilitates their binding to the negatively charged surface of the bacteria which may result in an enhancement of the bactericidal effect [6]. The shape of the nanoparticles also influences their antimicrobial effects [15,16]. In this article, we focused on the latest findings about antimicrobial activity of the most commonly employed nanometals and their mechanism of action.

Owing to the promising development and the vast application of nanoparticles, understanding the nanotoxicity and its outcomes is necessary. For years, pharmaceutical sciences have used nanoparticles to reduce toxicity and side effects of the drugs; nevertheless, there are some safety concerns about the nanoparticles. According to the reports, neurological and respiratory damage, circulatory problems and some other toxicity effect of nanoparticles are the main concerns in use of the nanoparticles [17–19]. Indeed, several types of the nanoparticles appear to be non-toxic and some of them are rendered non-toxic with beneficial health effects [20]. Appling antimicrobial activity of the nanoparticles to eradicate bacterial infections could be considered as one of these valuable health issues.

## 2. Ag and $Ag_2O$ nanoparticles

According to literature Ag nanoparticles are the most popular inorganic nanoparticles used as antimicrobial agents [21]. The antimicrobial application of Ag additives is widely benefitted in the various injection-molded plastic products, textiles and coating-based usages [22]. Ag nanoparticles also possess a range of biomedical applications [2]. It has been revealed that, Ag nanoparticles show a high antimicrobial activity comparable with its ionic form [23]. It has also been demonstrated that Ag nanoparticles are potential antimicrobial agents against drug-resistant bacteria [1]. According to literature, antibacterial action of Ag nanoparticles results from damage of the bacterial outer membrane [24]. Some researchers suppose that, Ag nanoparticles can induce pits and gaps in the bacterial membrane and then fragment the cell [25, 26]. It has also been known that Ag ions interact with disulfide or sulfhydryl groups of enzymes that lead to disruption of metabolic processes which in turn cause the cell death [22].

Jo et al. investigated the effect of size reduction on the antimicrobial effect of Ag nanoparticles. They used Ag nanoparticles to control *Bipolaris-sor Okiniana* and *Magnaporthe Grisea*. Similarly, they also evaluated the efficacy of Ag nanoparticles on different types of pathogens such as soilborne fungi which rarely produce spores. According to their results, Ag nanoparticles (20 to 30 nm) could better penetrate and colonize within the plant tissue. They suggested that, Ag nanoparticles had a great potential for use in controlling spore-producing fungal plant pathogens. They suggested that these nanoparticles might be less toxic than synthetic fungicides [23]. In the other study, Mie and et al. tested the antibacterial activity of their synthesized Ag nanoparticles (19 nm) against eight micro-organisms using the disk diffusion method. Their results revealed that the Ag nanoparticles showed potential antibacterial activity against Gram-negative bacteria. Thus, the authors suggested that these synthesized Ag nanoparticles could be applied in the pharmaceutical and biomedical industries [27].

Hernández-Sierra et al. reported comparative investigation of the bactericidal activity of Ag nanoparticles, ZnO, and Au on *Streptococcus mutans* (*S. mutans*). Their results indicated that Ag nanoparticles exhibited the most activity for controlling *S. mutans*. The authors suggested that Ag nanoparticles could be used in dental caries since it commonly is caused by *S. mutans* [28]. Likewise, Besinis et al. investigated the antibacterial effect of Ag nanoparticles on *S. mutans*. Their results showed that the antibacterial effect of Ag nanoparticles against *S. mutans* was more superior than that of chlorhexidine [11].

Zarei et al. evaluated antibacterial effect of Ag nanoparticles against four foodborne pathogens namely *Listeria monocytogenes, Escherichia coli* (*E. coli*), *Salmonella typhimurium* (*S. typhimurium*) and *Vibrio parahaemolyticus*. According to their results, Ag nanoparticles had great antibacterial effect on the mentioned pathogens. They concluded that Ag nanoparticles could be a good alternative for cleaning and disinfection of equipment and surfaces in the food-related environments [29].

Beside the particle size reduction, shape-dependent properties of nanoparticles have also been investigated by researchers. Pal et al. reported the shape dependent antibacterial activity of Ag nanoparticles (in three different forms: spherical, rod-shaped and truncated triangular). According to their findings, truncated triangular nanoparticles were more reactive due to their high-atom-density surfaces, and therefore showed higher antimicrobial activity [15]. In the other study, Bera et al. stated the size and shape-dependent antimicrobial activity of fluorescent Ag nanoparticles (1–5 nm) against Gram-positive (*Staphylococcus epidermidis* and *Bacillus megaterium*) and Gram-negative bacteria (*Pseudomonas aeruginosa*). They emphasized that the shape and size of the particles controlled their activity. According to these investigations, the smaller particles easily penetrated the cell wall and showed the enhanced antimicrobial activity. The authors suggested that these Ag nanoparticles could be used for different purposes such as clinical wound dressing, bioadhesives, biofilms and the coating of biomedical materials [16].

Bahrami prepared Ag–Au alloy nanoparticles to evaluate their antimicrobial effect against *Staphylococcus aureus* (*S. aureus*). The antibacterial activity of Ag–Au alloy nanoparticles was intensified when they combined with penicillin G and piperacillin. The authors suggested that Ag–Au alloy nanoparticles could be used as an adjuvant in combination therapy of antibiotics [30].

$Ag_2O$ nanoparticles have also been discovered to have great antimicrobial activity [1]. It is believed that, metal oxide nanoparticles might be considered as a novel alternative to the most antibiotics [1,31]. Sondi and Salopek-Sondi demonstrated antimicrobial efficacy of $Ag_2O$ nanoparticles against *E. coli*. They proposed that when *E. coli* were exposed to these nanoparticles, DNA lost its replication ability and the cell cycle halted at the $G_2$/M phase owing to the DNA damage. Then the cells were affected by oxidative stress, and apoptosis was induced [32].

Furthermore, Ag had reported to be less toxic than many other disinfectants. Marambio-Jones and Hoek had reviewed the antibacterial mechanisms of the Ag nanoparticles and potential implications for human health and environment [33]. We think that further research should be performed to develop Ag compounds, composites and alloys with the minimum toxicity and maximum antimicrobial effect.