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Short Commentary
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Therapeutic Efficacy of Silver Nanoparticles Against Antimicrobial Resistant Infections

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Abstract

In epoch of science and technology, incorporation of nanotechnology and utility of nanoparticles in various fields of medicine gained a lot much popularity. Besides many areas management of antimicrobial resistant (AMR) and multi drug resistant (MDR) infections with silver nanoparticles came up like a breakthrough to combat this Global health challenge. The objectives of this short commentary are to identify the therapeutic efficacy of silver nanoparticles (AgNPs) to manage AMR and MDR infections. It is concluded AGNPs because of specific characteristics i.e small sizes, spherical shapes, bio-caps, positive charges and production of reactive oxygen species exhibit significant inhibitory potential to kill MDR bacterial pathogens whether Gram positive or Gram negative.

Keywords: therapeutic efficacy; nanotechnology; silver nanoparticles; antimicrobial resistance; multi drug resistance; bacteria

Introduction

In the epoch of modern science and technology, overuse of high potency antibiotics to treat uncomplicated infections, had resulted in emergence of anti-microbial resistance. The scenario is further worsened by emergence of multi drug resistance even to commonly used antibiotics. In view to combat the challenging situation, clinicians, scientists and pharmaceutical accompanies are devoted to identify the solutions of denigrated happenstance [1]. Amongst discovery of new innovations for therapeutic strategies, nanomaterial-based antimicrobial, anti-inflammatory, anti-angiogenesis, and anti-cancer utility is harboring owing implication [2].

The due significance of nanomaterials renders to their specific chemical/physical properties, infinitesimal size, and arduous interactions with other materials. Further elaborating, nanocomposites are used to inhibit microbial growth. These are the combination of small particles of metals, metal oxides, and organic materials. Due to all these specific characteristics, their safety margin is concluded to be more when used as nano biotics to combat resistant life-threatening bacterial infections. However, bacterial sensitivity varies due to variation in growth phase, multiplication time, planktonic, and biofilm formation abilities. Other factors effecting efficacy of nano materials includes surrounding environment, humidity, air circulation, pH levels, and temperature. The nanoscale particles (NPs) are currently under successful trials for many purposes i.e anti-microbial agents, diagnostics, antimicrobial coatings over implantable devices, anti-inflammatory agents to promote wound healing, and enhancing antibiotic distribution. Besides desirable outcomes, trials for their undesirable effects in terms of real-life toxicity are going on to exactly identify the risks versus benefits [3].

The mode of action of NPs concluded so far included induction of oxidative stress, release of metal ions, and non-oxidative mechanisms. The resultant effect will be the bacterial gene mutation, thus, emergence of anti-microbial resistance (AMR) to specific NPs will be difficult and negligible. [4] The nano biotics employ organic-based liposomes and capsules, which are filled with nano-carriers i.e conventional antibiotics or novel RNAs. They exploit the cation leaching from metal colloid surfaces to act as antimicrobial agent. The commonly used metal colloids i.e silver, copper, gold etc can be engineered. Their particle size used to be <15nm to enhance passive diffusion across bacterial cell wall and other intracellular membranes. However, the metal colloids measuring >50 nm particle size will empower extended duration of cation leaching in either the biological or environmental matrices [3].

The nanoparticle engineering brought the revolution in field of nanotechnology, rendering the significance to manage infectious diseases, specifically of AMR etiology. The tarnished nanoparticle-based delivery podia include polymeric nanoparticles, liposomes, dendrimers, and inorganic nanoparticles. Thus, imparting excellent outcomes in treating and rapidly diagnosing complicated bacterial infections. It is anticipated that nanotechnology will endure progression in antimicrobial delivery systems for effectual, patient-compliant, and cost-effective approach [3, 4].

A published report for the year 2024 emphasized the usage of alternative approaches to manage AMR cases using nanoparticle-mediated immunotherapy. The mode of action involves destruction of neutrophils, in view to eliminate *Staphylococcus aureus.* The nanoparticles consist of naftifine, haemoglobin (Hb) and a red blood cell membrane coating. The biosynthesis of staphyloxanthin is inhibited by naftifine, bacterial hydrogen sulfide reduction is done by Hb and modification in bacterial lipid composition i.e lipid peroxidation is done by red blood cell membrane [5].

The emergence of AMR infections poses a noteworthy health burden around the Globe. A published surveillance report by world health organization (WHO), for antibiotic consumption tabulated the bacterial list posing high mortality rates. They include *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species [6]. The currently used antimicrobials are heading towards extremely limited effectiveness against these common microorganisms. A published report for the year 2024, narrated utility of silver nanoparticles (AgNPs), as an alternative promising one for combating bacterial infections [7]. The silver NPs have wide range of applications, starting from nanotechnology, nanomedicine, nano-medical imaging, biosensing, treatment of skin burns, and cancer treatment. Broadly covering the mode of actions focusses their physicochemical binding to cell surface resulting in membrane damage and destabilization. The release of free radicals and generation of reactive oxygen species (ROS) causes damage to cellular structures, inactivation of microbial enzymes, proteins, and nucleotides ultimately killing MDR bacteria. Besides, AgNPs also plays important role in minimizing oxidative stress in the human body [2, 8].

Literature Review

The Global statistics from AMR mortality revealed 4·95 million deaths in 2019. Besides the morbidity and mortality influence, it is predicted that till 2030, annual gross domestic product (GDP) losses will range from US$1 trillion to US$3.4 trillion [9].

Therefore, a dire necessity comes in lime light to identify parallel ways for combating the worsening scenarios. A ray of hope started arising by getting statistics and desirable outcomes of using silver NPs as therapeutic alternative option to manage AMR infections [7,8].

A published study by *Girma A etal; 2024,* showed promising results of using bio-capped silver nanoparticles (AgNPs). The desired outcomes were observed against both Gram-positive and Gram-negative multi drug resistant (MDR) bacteria. The minimum inhibitory concentration (MIC) was concluded to be 2.50 μg/ml to 100 mg/ml and 3.8 μg/ml to 2.5 mg/ml. While the minimum bactericidal concentration (MBC) and zone of inhibition (ZOI) were 4 to 25 mm respectively [8]. Besides this the particle size, shape, stabilizing agent, type of capping, surface charge, exposure time, pH, concentration, and type of bacterial, all can affect antibacterial activities of AgNPs. The mode of action of AgNPs involves damage of cell wall and cell membrane, degradation of biomolecules i.e lipids, proteins, and DNA, disruption of electron transport chain, and proton motive force. Moreover, green-synthesized AgNPs i.e formulated by synergistic effect between AgNPs and natural compounds, exhibited substantial antibacterial even against the MDR bacteria [8].

Many published studies had concluded in vitro and in vivo_concluded the safety margin and effective outcomes regarding usage of metallic NPs drug-resistant bacterial pathogens [10]. Various highlighted contributing factors for metallic NPs especially AgNPs includes particle size, shape, stabilizing agent, type of capping, pH, surface charge, concentration, exposure time, type of bacterial and colloidal state [11].

Particle size

A published report by *Cacai et al; 2023*, showed that <10nm particle size used to have increased bactericidal activity as compared to a particle size of >20nm [11]. Similarly, Dong et al.2019 also concluded same correlation i.e decreasing the aprticle size will increase the minimal inhibitory concentration and bactericidal activity. Thi sis due to increased surface area to volume ratio, ultimately facilitating higher plasma concentration of Ag^{+} ions [12].

Particle shape

A study carried out by *Acharya et al; 2021*, narrated those distinct shapes of AgNPs harbours varying degree of power for killing the bacteria. The study concluded anti-bacterial variation of four shapes of AgNPs i.e spherical, rod, triangular, and hexagonal. The spherical AgNPs were found to have highest antibacterial activity against Klebsiella p*neumoniae*. The larger effective contact area along with higher reactive facets were the imparting reasons for said property [13].

Capping and stabilizing agents: The capping / stabilizing agents plays a pivotal role for the stability and preventing agglomeration and steric hindrance. Besides this, while stabilizing their interaction, they cause alteration in the biological activity and surface chemistry of AgNPs within the preparation medium [14].

Exposure time

A published data by *Emery DD et al*, described that a bacterial time-kill curve analysis based upon the presence of AgNPs depends upon the incubation time. He concluded that bacterial count of *Salmonella enterica* serotype *Enteritidis* was reduced after 30 min of interaction as compared to 10 min of contact [15]. Similarly, *Fernández G, et al* reported same findings i.e intense effect on growth when exposed to longer period from 1 to 24 hrs showing increased zone of inhibition. Increased dispersing property on agar medium is the main reason imparting this phenomenon [16].

Surface charge

The surface charge of AgNPs influence the ability to kill microorganisms. The presence of positive charge was found to exhibit highest bactericidal activity as compared to negative charge. While neutrally charged AgNPs show intermediate antibacterial activity [17]

The pH of the medium plays an important role in the size and antibacterial activity of AgNPs. A published study by *Fernandes et al.* showed the impact of medium pH on the synthesis of nanoparticles with specific shapes and sizes. The results of study showed that the maximum antibacterial activity was observed at pH level 9 as compared to pH level 5 [18]. Another published study showed that big nanoparticles were produced at a pH of 5, as compared to a pH of 11, in which very tiny scattered nanoparticles were formed. High reduction rate at high pH can be the justified reason. Moreover, at low pH,5 oxidation will occur instead of reduction [19].

Concentration

The concentration of AgNPs is an added essential factor for their toxic effect. A dose-dependent antibacterial activity of AgNPs against Methicillin resistant Staphylococcus aures (MRSA) and non-MRSA are reported at a concentration of 12.5 mM. This shows that the inhibition zone is directly proportional to increase in concentration of AgNPs. The justification can be the release of more Ag^{+} ions when used in larger concentration and thus, yielding increased cellular oxidative stress, with higher antibacterial activity [20].

Bacterial type

It was discovered that bactericidal properties of AgNPs were more enhanced when used against Gram-negative bacteria as compared to Gram-positives one. The reason could be the thin peptidoglycan layer i.e 7–8 nm of Gram-negative bacteria as compared to 20–80 nm thickness of Gram-positive bacteria [20].

Conclusion

It is concluded that AGNPs because of specific characteristics i.e small sizes, spherical shapes, bio-caps, positive charges and production of reactive oxygen species exhibit significant inhibitory potential to kill MDR bacterial pathogens whether Gram positive or Gram negative.

Recommendations

Silver nanoparticles can be used as an alternative to antibiotics for their antimicrobial properties. The pharmaceutical companies, clinicians, microbiologists and clinicians should work in collaboration to identify the exact therapeutic dose for AMR/MDR pathogens. The pharmaceutical companies, clinicians, microbiologists and clinicians should work in collaboration to identify the diagnostic efficacy of AgNPs for early diagnosing AMR/MDR pathogens. Large scale randomized clinical trials are required to assess the safety / toxicity of AgNPs to human cells. Lare scale studies are required to identify the mechanism for pathogen resistance to AgNPs, study of synergistic effect by combining AgNPs with low doses of common antibiotics with greater antibacterial activity and development of new silver-based gel having 100% effective outcome for MDR bacteria. Large scale studies are required to assess the utility and effectiveness of various NPs to manage other microbial infections i.e viral, parasitic, fungal and mycobacterial.

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