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Mini Review

Exploring ZnO Nanoparticles in Antibiotic Therapy

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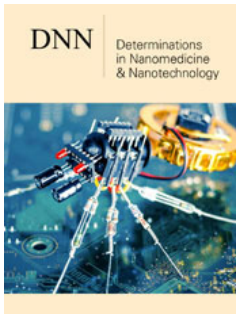

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Abstract

Today, the raise in the rate of infectious diseases and the emergence of Multidrug-Resistant (MDR) bacteria has resulted in an increased number of associated hospital-acquired and community-acquired infections and mortality, so there is an urgent need to develop alternative antimicrobial strategies. For this purpose, zinc oxide nanoparticles (ZnO NPs) have demonstrated potent antibacterial activity and biocompatibility. In contrast to the conventional antibiotics, they are able to inhibit or interfere with bacterial Quorum Sensing (QS) and biofilm formation. Also, they are less sensitive to the development of resistance towards microorganisms. In addition, their zinc's immunomodulatory effects contribute to the antimicrobial activity of conventional antibiotics. Moreover, there have been reported synergistic effects of ZnO NPs with various antibiotics. However, it is important to note that even though ZnO NPs have a wide range of antibacterial activities toward various microorganisms; their antimicrobial properties depend on the different morphologies, size and shape they have. Finally, although there have been proposed different mechanisms through which ZnO NPs exert their antimicrobial action, they are not yet fully understood.

Keywords: Zinc oxide nanoparticles; Antibiotic therapy; Infectious diseases; Multiple drug resistance

Abbreviations: MDR: Multidrug-Resistant; ZnO NPs: Zinc Oxide Nanoparticles; QS: Quorum Sensing; IL-8: Cytokine-8; PMNs: Polymorphonuclear Leukocytes Cells; PK: Pancreatin Enzyme; MRSA: Methicillin Resistant Staphylococcus Aureus; ROS: Reactive Oxygen Species; NO: Nitric Oxide; GAL: β-Galactosidase; AMR: Antimicrobial Resistance

Introduction

There is an urgent need to develop new and effective antibiotic agents to combat infectious diseases because bacterial infections and multiple drug resistance are the leading causes of death in the world [1]. In this respect, nanomaterials are a promising alternative. Among these materials, metal and metal oxide nanoparticles, especially zinc oxide nanoparticles (ZnO NPs), stand out for their advantageous properties including bactericidal and bacteriostatic activities against a broad spectrum of pathogens [2,3]. Furthermore, ZnO NPs are considered by the U.S. Food and Drug Administration (FDA) as safe materials for human health (Generally regarded as safe- 21CFR182.8991) for what they have numerous applications in the medical, biomedical and cosmeceutical industry [4]. Zinc is not only an indispensable trace element involved in normal growth, bone metabolism, pathways and cell signaling, but can also manipulate immune defense against bacterial infection through its immunomodulatory effect [5]. ZnO NPs have been shown to enhance the antibacterial activity of the organism by their ability to promote a proinflammatory response by activating monocytes, releasing of cytokine-8 (IL-8) from epithelial cells and stimulating the phagocytosis and degranulation processes of Polymorphonuclear Leukocytes Cells (PMNs). For example, Wang et al. [6] found that nano-ZnO films were able to promote the phagocytic capacity of macrophages and the stimulation of inflammatory cytokine release in a dose-dependent manner. In addition, the ZnO NPs showed activity against biofilms of adherent bacteria. Authors found that the combination of the direct bacterial killing property of ZnO NPs and their indirect immunomodulatory properties led to a synergistic antimicrobial activity.

ZnO NPs have also stood out for enhancing antibiotic efficacy against different pathogenic microorganisms when combined with antibiotics such as β-lactams, cephalosporins and aminoglycosides [7]. For example, Rashmi et al. [8] found synergistic antibacterial activity of ZnO NPs when were combined with the β-lactam antibiotics cefotaxime, ampicillin, ceftriaxone and cefepime, respectively, against *E. coli, K. pneumoniae, S. paucimobilis, and P. aeruginosa*, respectively. They found that ZnO NPs enhanced the β-lactam antibiotics bactericidal activity between 50% and 85% times the antibiotic activity of these conventional antibiotics alones. Abo-Shama et al. [9] observed also a synergic effect of the antibiotics azithromycin, oxacillin, cefotaxime, cefuroxime, fosfomycin and oxytetracycline against *E. coli* in combination with ZnO NPs and also with azithromycin, cefotaxime, cefuroxime, fosfomycin, chloramphenicol and oxytetracycline against *S. aureus* compared to antibiotics only. Even though the mechanism of ZnO NP's synergistic action in association with conventional antibiotics remains under investigation, different mechanisms have been proposed. For example, Eleftheriadou et al. [10] suggested that the synergistic effects of ZnO NPs in combination with the antibiotic ciprofloxacin, known to be subject to bacterial efflux, against MDR clinical strains of *S. Pseudomonas aeruginosa* could be attributed to an inhibition of bacterial efflux pumps of in a concentration-dependent manner, promoting the antibiotics intracellular accumulation. Mistry et al. [11] proposed that the synergistic effect of ZnO NPs on the antibiotic activity of rifampicin against the wild type and laboratory-generated *Mycobacterium smegmatis* and also against *M. bovis* is due to an increased damage of the bacterial membrane and an increased accumulation of rifampicin inside the cell leading to the loss of cell viability.

Moreover, Banerjee et al. [12] developed ZnO NPs surface doped with Pancreatin Enzyme (PK), denoted as ZnO NPs-PK, which were able to impaired initial and mature biofilms formation of Methicillin Resistant *Staphylococcus Aureus* (MRSA) known to be a strong biofilms producer. The ZnO NPs-PK demonstrated superior antibacterial, anti-biofilms and anti-virulent activities against MRSA in comparison to ZnO NPs or PK alones. Eshed et al. [13] reported that ZnO NP-coated teeth showed significant reduction in *Streptococcus mutans* biofilm formation by 85%, but without bacteria growth inhibition. This phenomenon was attributed to a protection mechanism of the bacteria against the generation of Reactive Oxygen Species (ROS). It is also noteworthy the antimicrobial activity of ZnO NPs against fungi, parasites, viruses, and both Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* indirectly through the generation of nitric oxide (NO), a broad-spectrum antibacterial agent, by catalytically decomposing both endogenous (S-nitrosoglutathione) and exogenous (β-gal-NONOate) donors of NO at physiological conditions due to the innate glutathione peroxidase and glycosidase activities of ZnO NPs [14].

Different reports suggest that the antimicrobial activity of ZnO NPs depends on both their particle size and shape. Specifically, Raghupathi et al. [15] obtained ZnO NPs of various particle sizes covering a range between 12 and 307nm examining their antibacterial activities. Authors found that ZnO NPs that demonstrated the highest antibacterial activity were those of smaller size (12nm). Furthermore, authors found that ZnO NPs larger than 100nm did not have significant growth inhibition of the strain methicillin sensitive *S. aureus* RN 6390 at the concentration of 6mM. They concluded that the antibacterial activity of the ZnO NPs was inversely proportional to the size of the ZnO NPs. On the other hand, they found that the antibacterial activity against *S. aureus* was due to the action of the ZnO NPs rather than to the Zn^{+2} ions dissolving from these nanoparticles. In addition, they suggested that although ZnO NPs have a broad activity against different microorganisms, their antibacterial activity was differentiated according to the structural differences between microorganisms. On the other hand, Sang-Ho Cha et al. [16] reported that the inhibitory activity and binding with the β-Galactosidase (GAL) enzyme are dependent on the ZnO NPs shape. Authors found that the strongest inhibition activity was observed for ZnO nanopyramids in comparison to the hexagonal, nanoplates, and nanospheres geometrical shapes, reflecting the strong shape-specific antibacterial activity against methicillin-resistant *Staphylococcus Aureus* (MRSA). ZnO-based NPs also stand out for their Quorum Sensing (QS) inhibition and biofilm formation. Khan et al. [17] development ZnO nanospikes in the diameter range of 40-130nm and evaluated their inhibitory effect on QS and biofilm formation produced by the two Gram-negative bacteria *Chromobacterium violaceum* (strains 12472 and CVO26) and *P. aeruginosa* (PAO1). Authors found that ZnO nanospikes enhanced the antibiotic efficiency and decreased the pathogenicity of the tested bacterial pathogens, being the finest one that had the higher inhibitory action on the virulence factor productivity. Also, Alavi et al. [18] found that ZnO NPs were able to inhibit biofilm formation and to reduce the pyocyanin concentration of *P. aeruginosa* ATCC 27853.

Conclusion

ZnO NPs are expected to be used in antibiotic formulations in the future due to their outstanding antibacterial, immunomodulatory and inhibitory properties of bacterial biofilm formation and virulence factors. Moreover, ZnO NPs have shown synergistic antimicrobial effects when combined with conventional antibiotics or enzymes. In addition, they are a promising therapeutic solution to combat the Antimicrobial Resistance (AMR) caused by pathogens resistant to conventional used antimicrobial drugs or antibiotics.

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