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Bactericidal Potential of Aluminium Oxide Nanoparticles: An Up-to-Date

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Abstract: According to WHO (2014) reports, antibiotic resistance is now a major threat to public health worldwide. Despite immense advances in antibacterial therapies and infection strategies, the emergence and reemergence of diverse bacterial infections and increased antibacterial resistance represents an emergency situation world. Unfortunately, there is no assurance that the development of new antimicrobial drugs can catch up to the microbial pathogen's fast and frequent development of resistance in a timely manner. Currently, metal oxide nanoparticles are the most promising tools applied as antimicrobial agents for diagnosis of diseases, drug delivery systems, sun screens and ceramics in biomedical and pharmaceutical arena. To date very little studies are available in literature on the interaction of alumina nanoparticles (Al_2O_3 NPs) with multi-drug resistant strains. Considering the paucity of earlier reports this review attempts to elaborate an up-to-date on the antibacterial properties and mode of action of Al_2O_3 NPs and its potential clinical applications.

Keywords: Multi-drug resistant, Al_2O_3 NPs, antibacterial properties

INTRODUCTION

The identification of infectious diseases caused by bacteria in the late 19th century stimulated the search for appropriate preventative and therapeutic regimens; however, successful treatment came only with the discovery and introduction of antibiotics half a century later. Antibiotics have revolutionized medicine in many respects, and countless lives have been saved; their discovery was a turning point in human history. Regrettably, the use of these wonder drugs has been accompanied by the rapid appearance of resistant strains. Antibiotic resistance–when bacteria change so antibiotics no longer work in people who need them to treat infections–is now a major threat to public health[1]. Antibiotic discovery, modes of action, and mechanisms of resistance have been productive research topics in academia and, until recently, in the pharmaceutical industry[2]. Unfortunately, there is no assurance that the development of new antimicrobial drugs can catch up to the microbial pathogen's fast and frequent development of resistance in a timely manner. For example, drug resistant infections

in hospitals and in the communities caused by both Gram-positive and Gram-negative bacterial pathogens are growing rapidly, and the continued evolution of antimicrobial resistance threatens human health by seriously compromising our ability to treat serious infections. Among gram-negatives, which are isolated in up to 80% of polymicrobial bacteremias, *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa* remain the predominant species. Of particular challenge are the infections due to methicillin-resistant *Staphylococcus aureus* (MRSA), representing up to 50% of all staphylococcal infections; vancomycin-resistant enterococci (VRE), representing nearly 30% in the United States; extended-spectrum β-lactamase (ESBL)–producing gram-negative bacteria; and other multi-drug resistant (MDR) bacteria such as *Acinetobacter baumannii*, *K. pneumoniae* carbapenem-resistant (KPC), *P. aeruginosa* and fluoroquinolone-resistant *E. coli*[3]. These challenging and dynamic patterns of infectious diseases and the reemergence of these bacterial strains resistant to many currently used antibiotics demand for longer-term solutions to this ever-growing and foreseeable problem[4]. One of the recent efforts in addressing this challenge lies in exploring antimicrobial nanoparticles, to which microbial pathogens may not be able to develop resistance, and novel nanosized platforms for efficient antibiotics delivery. In the present scenario, nanoscale materials have emerged up as novel antimicrobial agents due to their high surface area to volume ratio and unique chemical and physical properties[5-6]. Recent studies explore that some metal nanoparticles exhibited excellent antimicrobial activities, which is utilized in controlling infectious diseases[7-9]. Antimicrobial nanoparticles (NPs) offer many distinctive advantages in reducing acute toxicity, overcoming resistance and lowering cost, when compared to conventional antibiotics[10]. Inorganic metal oxide NPs can be used as effective disinfectants in view of their non toxic profile, stability and antibacterial properties[11]. Metal oxide nanoparticles have large surface area as compared to their bulk counterparts offer better antimicrobial activity[12]. It is known that the size of bacterial cell ranges in the micrometer while its outer membranes have pores in nanometer range. The size of nanoparticles are smaller than the bacterial pores, thus smaller size NPs can easily penetrate the bacterial membrane[13]. The antibacterial activites of metal oxide NPs such as ZnO towards ESBL-producing *E. coli*, *K. Pneumoniae* and MRSA were already reported[14,15]. Compared to the previous published reports on various applications of aluminium oxide nanoparticles (Al_2O_3 NPs), limited work has been done on the antimicrobial activity of Al_2O_3 NPs[23]. Therefore, the present study has been made an attempt to find out the potential antibacterial effects of Al_2O_3 NPs against various gram positive and gram negative as well as MDR clinical isolates.

NANOTECHNOLOGY AS TREATMENT MODALITY: ANTIBACTERIAL ACTIVITY OF Al_2O_3 NPs

Al_2O_3 in particular possesses a variety of commercial and industrial uses and has become one of the most important commercial ceramic materials[16]. As a widely studied nanomaterial, Al_2O_3 NPs have been applied in catalysis[17], nanocomposites[18], polymer modification[19], functionalization of textiles[20], heat transfer fluids[21] and wastewater treatment[22]. In addition, Al_2O_3 NPs have featured in biological applications such as biosensors, biofiltration and drug delivery[22] and antigen delivery for immunization purposes[24]. Sadiq et al. investigated the antibacterial effect of alumina towards *E. coli*. The results indicated that alumina NPs had a mild inhibitory effect against *E. coli* at high concentrations upto 1000 μg/ml[25]. Jiang et al. also reported that Al_2O_3 NPs had a mortality rate

of 57% to *B. subtilis*, 36% to *E. coli*, and 70% to *P. fuorescens*[12]. Bala et al. synthesized alumina-silver[31] composite NPs by a simple, reproducible, wet chemical method, with the surface of the oxides modified with oleic acid. Preliminary antibacterial studies performed using disc diffusion assays against *E. coli* DH5α and *S. epidermidis* NCIMB 12721suggested that the composite nanomaterials have immense potential as antimicrobial agents[26].

Pakrashi et al. examined the cytotoxicity of Al_2O_3 NPs at very low concentration to a dominant bacterial isolate from freshwater, *B. licheniformis*. They found that the exposure to 1 μg/ml Al_2O_3 NPs for 2 h caused a 17% decrease in cell viability (as determined by plate count and MTT assay)[27]. Ravikumar et al. investigated the antibacterial activity of five metal oxide NPs including Al_2O_3 NPs against urinary tract infectious bacterial pathogens viz., Pseudomonas sp., Enterobacter sp., Klebsiella sp., *E. coli*, *Proteus morganii* and *S. aureus* by well diffusion and time kill assay methods. They reported that among five metal oxide NPs, Al_2O_3 NPs showed maximum sensitivity *E. coli* followed by Klebsiella sp and *P. morganii* respectively. The MIC results also revealed that Al_2O_3 NPs showed maximum inhibition at 5 μg/ml against *E. coli* followed by Klebsiella sp and *P. morganii* at 10 μg/ml, respectively[28]. Geoprincy et al. investigated that Al_2O_3 NPs showed a characteristic zone of inhibition against *B. subtilis* and *B. cereus* for 100 μg MIC of NPs, whereas no inhibitory effect was observed against *K. pneumoniae* and *Vibrio cholerae*[29].

Recently, we have carried out extensive studies on the antibacterial behaviour of Al_2O_3 NPs against gram-positive and gram-negative drug resistant bacterial clinical isolates. We investigated the antibacterial effect of alumina towards *S. aureus* ATCC 25923, methicillin-sensitive S. aureus (MSSA), and MRSA strains and growth inhibition was studied at varied concentrations (0, 250, 500, 1000, and 2000 μg/ml) of Al_2O_3 NPs[30]. The growth curves of bacterial cells treated with Al_2O_3 NPs indicated that it could inhibit the growth and reproduction of bacterial cells. It was found that at all these concentrations; the NPs caused a growth delay of all tested strains of *S. aureus*. In the absence of Al_2O_3 NPs, *S. aureus* reached exponential phase rapidly. The bacterial growth of the cells treated with 250 μg /ml Al_2O_3 NPs was also slightly lower than that of cells in the control group. However, NPs with highest concentration (1000 and 2000 μg/ml) showed almost negligible growth for up to 8 h for *S. aureus* ATCC 2592, MSSA, and MRSA, representing good bacteriostatic activity at lower concentration and bactericidal activity at higher concentration (2000 μg/ml) of Al_2O_3 NPs[30].

In another study, we have also done extensive work on the antibacterial activity of Al_2O_3 NPs against 80 nonrepetitive clinical isolates of ESBLs positive and ESBLs negative *E. coli* and studied the membrane permeability of the NPs towards these organisms[13]. We observed that the bacterial growth was inhibited at 500 μg/ml after 4 h treatment. As the concentrations of Al_2O_3 NPs increases (i.e., at 1000 and 2000 μg/ml), almost no growth were seen in *E. coli* ATCC 25922, ESBL-producing and non-ESBL isolates after 8 h treatment[13].

POSSIBLE MECHANISMS OF ANTIBACTERIAL ACTION BY Al_2O_3 NPs

Ansari et al. have done extensive work on the mode of action of Al_2O_3 NPs using SEM, HR-TEM and FTIR analyses against *E. coli* and *S. aureus*[13,30]. The morphology of bacterial cells changed after the treatment of NPs and NPs were found to be clustered on the cell surface as seen under

SEM analysis (Figure 1). HR-TEM analysis shows that small size NPs penetrate inside the cells which cause perforation and formation of pits on their surfaces; whereas the agglomerated NPs remain adhered to the outer membrane (Figure 2). Bacterial membrane with distorted morphology exhibits an increased permeability and altered transport mechanism, which ultimately leads to cell death[31]. The toxic effects of Al_2O_3 NPs has been partially explained based on their dissolution producing Al ions in NPs suspension with the release of reactive oxygen species[32]. However, we have reported that the impairment of cell membrane integrity is the major cause of bacterial death. One of the possible reasons for the damage could be direct interaction between Al_2O_3 NPs and the external membrane surface[30]. The effects of size on antibacterial properties of nanoparticles have already been reported in the literature[33-34]. It was also suggested that bacterial toxicity may be because of small size of NPs i.e., Al_2O_3 NPs are much smaller than the bacterial cells, they coated around the bacteria cell by electrostatic attractive forces, neutralizing the bacterial surface charge and creating large aggregates (Figure 2). Negatively charged bacterial cells (a few micrometers in size), could readily capture NPs by electrostatic attractive forces, while it would be difficult to attract bulk particles[30].

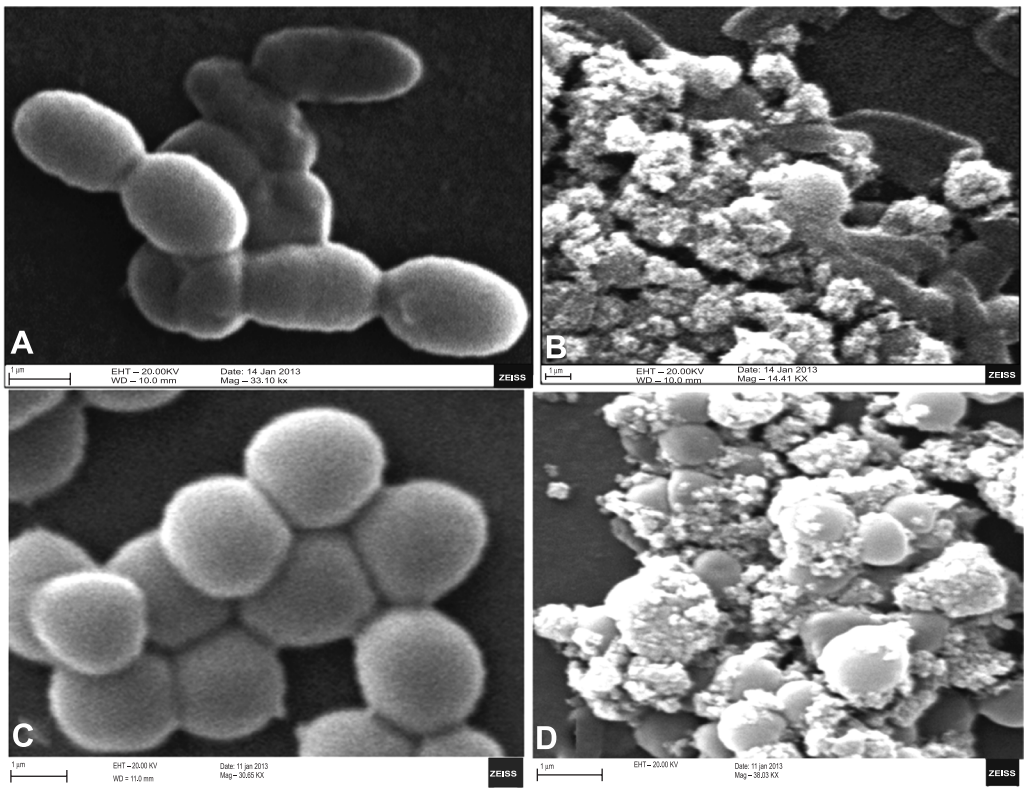


Figure 1: Scanning electron micrograph of *E. coli* & *S. aureus*: a & c control; b & d treated with Al_2O_3 NPs (Adapted from Ansari et al.)[13,30]

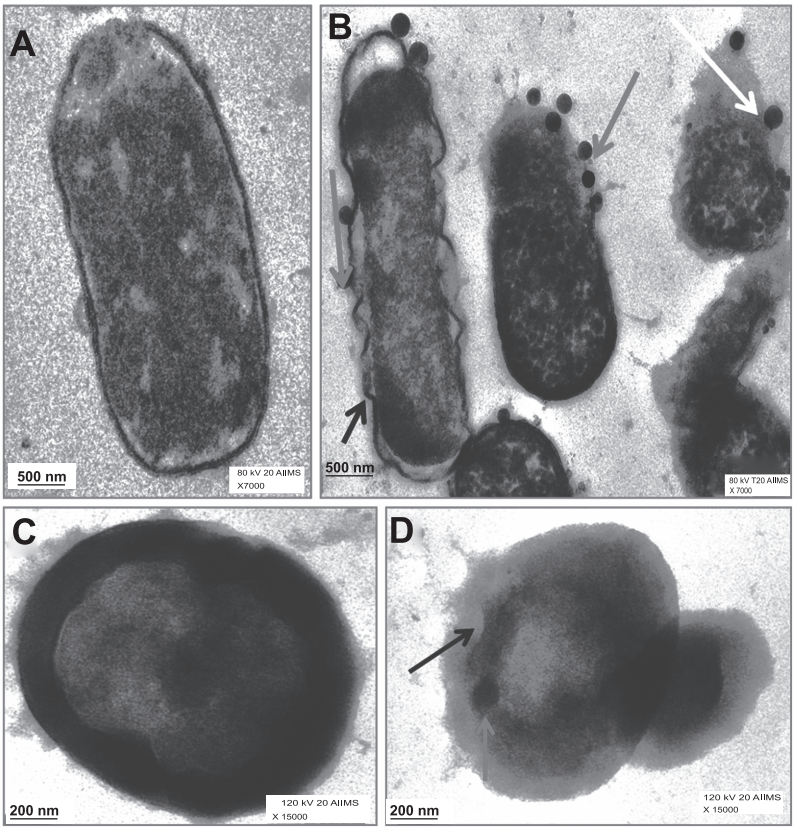


Figure 2: HR-TEM micrograph of *E. coli* & *S. aureus*: a & c control; b & d treated with Al_2O_3 NPs. Grey & white arrows indicate nanoparticles attachment on membrane surface and inside the cells, while black arrows indicate damaged membrane at various sites (Adapted from Ansari et al.) [13,30]

The mode by which the NPs interact to the bacterial surface and affect cell surface biomolecules is of great interest[13]. Lipopolysaccharides (LPS) are the major biomolecules in bacterial membrane which possibly interact with NPs. The interaction of NPs with bacterial biomolecules, change the physio-chemical properties of surface biomolecules may possibly a reason of NPs bacterial toxicity[13]. The ATR-FTIR study of Ansari et al showed change in chemical environment of the O-antigen sugar chain after LPS attaches to Al_2O_3 NPs. They also studied the Al_2O_3 NPs interaction with L-α-Phosphatidyl-ethanolamine (PE) and observed that the amine moiety of PE most likely interacts with the NPs. The breaking of the phosphodiester bond and fall-off phosphate groups also changes the amphiphilic nature of the PE, which may lead to disordered alkyl chains reflected by the CH_2 spectra[13]. The Al_2O_3 NPs induced structural changes in phospholipids may lead to the loss of amphiphilic properties, damage of the membrane and cell leaking[13].

CONCLUSIONS

Reemergence of multi-drug resistant pathogens such as bacteria, fungi, and viruses remain a major health concern worldwide. Based on the above studied, the mode of action of Al_2O_3 NPs may be described as Al_2O_3 NPs making a break through the permeability of outer membrane firstly, resulting in the leakage of cellular materials. HR-TEM image shows the particle binding and damage in cell wall. Al_2O_3 NPs adhered to the cell wall of bacteria and penetrated through the cell membrane. The interaction of Al_2O_3 NPs with bacterial membrane and damage to bacterial cell wall and their subsequent penetration inside the bacterial cell resulted in inhibition of cell growth and reproduction. The biomolecular and structural damage in LPS and PE suggested their role in augmenting Al_2O_3 NPs induced bacterial toxicity. It is concluded that the interactions between Al_2O_3 NPs and membrane amphiphilic biomolecules may alter the fluidity, integrity and lateral organization of bacterial membrane, which contributes significantly for effective antibiosis of NPs. In depth studies regarding the interaction of the NPs with cells, tissues and organs as well as the optimum dose required to produce therapeutic effects need to be ascertained before we can expect a more meaningful role of the Al_2O_3 NPs in medical application. More work is therefore needed to confirm these observations.

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