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RESEARCH ARTICLE

ALUMINIUM NANOMATERIALS AS DELIVERY SYSTEM IN COMBATING DISEASES

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ABSTRACT

Conventional chemotherapy against diseases develops multiple drug resistance and adverse side effects owing to inadequate drug therapeutic index, non-selective toxicity, insolubility and low bioavailability of drugs. In this context, metallic nanomaterials have emerged as potent effective delivery system against infectious diseases due to their nano, controllable sizes utilized as high surface area, enhanced reactivity and easy functionalizable structures. Aluminium nanomaterials (AlNMs) such as aluminium (Al^0) and aluminium oxide (Al_2O_3) due to their capability of generating reactive oxygen species (ROS) and surface-charge interactions with cells, are able to create oxidative bursts-oriented stress followed by damages to DNA, protein changes and lipid peroxidation resulting in adhesive infectious and microbial cellular deaths. This review is mainly focused on synthesis, drug loading, functionalization, mechanism of action, biomedical application, toxicity, biodistribution and elimination of aluminium nanomaterials as delivery system against different diseases.

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INTRODUCTION

Infectious diseases, whether intracellular or extracellular, medical device-associated or biofilm mediated, caused by viruses, bacteria, fungi and parasites, have been a worldwide problem for millions of demises each year (Morens and Fauci, 2013). Infectious diseases have been classified as emerging and re-emerging, while new diseases are assigned as emerging, and re-appearing diseases, owing to mainly drug resistance, are referred as re-emerging (Fauci and Morens, 2012). Direct / contagious or transmitted virulent infections are primarily prevented by host body's defense mechanisms such as anti-oxidant and immune defense systems (Mandal and Joardar, 2021). However, transmission of infections occurs after entry of few micro-organisms through natural orifices into the host cells and overcome host body's defense system, resulting in their replications inside the host cells to cause intra and extra cellular damages (National Institutes of Health [US], 2007). Generally, drug resistance interferes with the treatment of infectious diseases, indicating the need for new therapeutics to overpower drug resistance. The therapeutic agents such as metal nanoparticles due to their surface charges, small sizes (1-100 nm), capability to interact with biomolecules on cell-surfaces and within cells, and cell penetrating capability for their high surface area, have shown their microbicidal activity, resulting in cell death (Casadevall, 1996; Mody *et al*., 2010).

These nanoparticles may be conjugated with selected ligands, drugs, antibodies, enzymes and proteins for distinct binding functionality to selective target cells to improve their targeted drug delivery ability extending blood circulation time and therapeutic efficiency at the pathological site/s (Mody *et al*., 2010). Recently, aluminium nanomaterials (Al NMs) such as mainly aluminium (Al^0) and aluminium oxide (Al_2O_3) nanoparticles (NPs) for their suitable metallic physico-chemical properties have attracted attention as nano-biomedicinal drug delivery system against various diseases. Aluminium is abundant metal found on earth's crest, while thermo dynamically stable Al_2O_3 NPs possess the corundum-like structures with oxygen atoms and Al^{3+} ions, carrying the positive charges on their surfaces (Tavakoli *et al*., 2013). It is reported that Al_2O_3 NPs may induce oxidative stress via increased generation of reactive oxygen species (ROS) to injure cells (Li *et al*., 2012; Prabhakar *et al*., 2012; Morsy *et al*., 2013). The NPs that enter the body through the gastrointestinal tract, skin or respiratory system may translocate to other cells / tissues through different transfer routes or mechanisms, while their toxicity depends on their primary and secondary characteristics in biocompatible body fluids (Oberdorster *et al*., 2005; Li *et al*., 2009; Roy *et al*., 2014; Bruinink *et al*., 2015). Metal-based Al NMs may be designed for biomedical applications based on their higher stability, biocompatibility, target selectivity and non-toxicity-coating with or without ligands to utilize as antimicrobial agent against pathogen to disrupt cell membrane directly or form free radicals and to overcome drug resistance.

This review focuses mainly Al NMs as potential delivery therapeutics to treat infectious diseases and to get their higher biological efficiency.

Synthesis of aluminium oxide nanoparticles: Three types of Al_2O_3 NPs are synthesized by the modification of the method (Roh *et al*., 2011; Park *et al*., 2015). The starting materials include $Al_2(SO_4)_3.16H_2O$, $Al(NO_3)_3.9H_2O$ and urea. The Al_2O_3NPs are prepared at the concentration ratio (0.215) of $Al_2(SO_4)_3.16H_2O$ to $Al(NO_3)_3.9H_2O$ utilizing the forced hydrolysis method. In brief, 0.0015M $Al_2(SO_4)_3.16H_2O$, 0.007M $Al(NO_3)_3.9H_2O$ and 0.1M urea are admixed into 100 mL deionized water (DW). The solution is placed in an oil bath at 90◦Cfor 1 h for reaction. The crude product is cleansed several times with DW for removing SO_4^{2-} and NO_3^-. The yield γ-Al_2O_3 HNPs are then heat-treated in air at 900◦C and 1050◦C for 2 h for their transformations into γ-Al_2O_3NPs and α-Al_2O_3NPs respectively. These NPs are then dispersed into DW for further use. In another method, 56.6 mL hydrochloric acid (HCl) (36% v/v) and an equal quantity of DW are mixed at 10◦C. An approximate 40g aluminium foil is gradually adjoined into the reactor until effervescence stopped (equation 1).

$$HCl_{(aq)} + Al_{(s)} \rightarrow Al_2Cl_6(aq) + H_{2(g)} \quad 1$$

The solution is filtered for removing impurities and then cooled. 1M sodium carbonate (Na_2CO_3) is then gently adjoined into the filtrate for precipitating the Al_2O_3 ensuring the conversion of all aluminium chloride (Al_2Cl_6) to Al_2O_3 (equation 2).

$$Al_2Cl_{6(aq)} + 3Na_2CO_{3(aq)} \rightarrow 3CO_{2(g)} + Al_2O_{3(s)} + 6NaCl_{(aq)} \quad 2$$

More amount of DW is added to Al_2O_3 and left for 1 h. The settled clear liquid solution is decanted and more DW is added, and repeated this process to wash off the sodium chloride (NaCl). The solution is then filtered to get Al_2O_3 and dried in an oven at 100◦C for 3-4 h for the removal of water. Mechanical milling is applied to crush and reduce the particles into NPs and sieved utilizing various pore-sized sieves.

Characterization of aluminium nanomaterials: The absorption bands (280-400 nm) of the synthesized NPs dissolved in n-hexane solution are determined by utilizing UV-VIS spectroscopy. The size, composition, morphology and crystalline phase of the AlNMs are determined by using transmission electron microscopy and X-ray diffraction. The hydrodynamic diameter, surface charge or zeta potential of the NPs are determined by utilizing dynamic light scattering. The functional groups of the NPs are investigated by utilizing Fourier-transform infrared spectroscopy.

Mechanism of action of aluminium nanomaterials: Thermodynamically stable aluminium NPs possess corundum like structure with oxygen atoms adopted hexagonal packing with aluminium ions filled 2/3 rd of the octahedral sites in the lattice (Sadiq *et al*., 2009). The NPs may be contacted with cells through electrostatic attractions, hydrophobic interactions, van der Waals forces or receptor-ligand bindings (Wang *et al*., 2017). NPs can bind, cross or penetrate the cell membrane owing to their larger surface to volume ratio and generate ROS and interact with cellular basic ingredients such as DNA, ribosomes, lysosomes, enzymes and biomolecules leading to oxidative stress-triggered electrolyte balance disorders, heterogeneous alterations, changes in cell membrane permeability, enzyme inhibition, protein deactivation, changes in gene expression and mitochondrial or cytoplasmic leakage, resulting cellular damages or death (Wang *et al*., 2017).

Aluminium ions (+ve charge) released from Al_2O_3 NPs are absorbed via the cell membrane (-ve charge) followed by the direct interactions with the functional groups of nucleic acids and proteins such as amino (-NH), carboxyl (-COOH), phosphate (-PO4) and mercapto (-SH) groups or ε-poly-L-lysine to damage or disturb enzymatic activity, cell structure in the phospholipid or physiological processes, and ultimately cellular death (Wang *et al*., 2017). Aluminium NPs as adjuvants due to their adsorbance characteristic to antigens for the development of vaccine for cancer treatment are utilized to induce a stronger balanced (Th1/Th2) immune responses associated with an enhanced number of cytotoxic $CD4^+$T and $CD8^+$T cells in peripheral blood, and a marked enhancement in antibody titre and hemagglutination inhibition (Nazarizadeh *et al*., 2022).

Biomedical applications of aluminium oxide nanoparticles: Al_2O_3NPs have been utilized in various biomedical applications against infections and diseases (Hassanpour *et al*., 2018; Ranghar *et al*., 2014; Aderibigbe, 2017; Nikolova and Chavali, 2020).

Anti-microbial activity: Several researchers have reported that Al_2O_3NPs (>1000 μg/mL) have shown their microbicidal anti-growth activity as well as reduced extracellular protein content owing to their large surface area and electrostatic interactions through direct attachment to the microbial cell walls, leading to the distortion of the cell membranes and cell death (Hassanpour *et al*., 2018; Ranghar *et al*., 2014; Aderibigbe, 2017; Nikolova and Chavali, 2020). Other investigators have exhibited that aluminium-silver (Al_2O_3-Ag) nanocomposite modified by oleic acid as capping agent to attach the AgNPs have been utilized for enhanced anti-microbial activity evaluated by disc diffusion assays (Ranghar *et al*., 2014; Nikolova and Chavali, 2020). Another study has indicated that Fe_3O_4/Al_2O_3 core/shell magnetic NPs have shown their magnetically-derived photothermal killing activity on gram -positive/negative and drug-resistant microbial strains through magnetic field-induced microbial cells-recognition (Hassanpour *et al*., 2018).

Drug delivery: Few researchers have exhibited that mesoporous Al_2O_3NPs loaded with telmisartan have been used as vehicle to deliver drug against blood pressure (Hassanpour *et al*., 2018). Several other investigators have shown that sol-gel of Al_2O_3NPs loaded with ibuprofen have been utilized for the treatment of inflammatory diseases as an efficient drug delivery carrier (Hassanpour *et al*., 2018).

Cancer treatment: Several researchers have indicated that spherical Al_2O_3NPs have anti-cancer characteristics, as well as Al_2O_3 nanotubes loaded with thapsigarin and 3-methyladenine have been utilized to target autophagy signaling in cancerous cells as drug delivery vehicle for the treatment of cancer (Hassanpour *et al*., 2018). Other investigators have exhibited that poly-glutamic acid modified Al_2O_3NPs have shown their cytotoxic activity by inducing cell death in human prostate cancer cells through induction of ROS and subsequent mitochondrial dysfunction (Hassanpour *et al*., 2018). Another study has indicated that nanopetal Al_2O_3 have shown decreased viability against mouse neuroblastoma Neuro-2a cells (Hassanpour *et al*., 2018). Few other investigators have utilized Al_2O_3NPs as efficient adjuvant in cancer immunotherapy by using as cancer antigen vehicle to autophagosomes of dendritic cells in the presentation of antigens to T lymphocytes to enhance their activated number for cancer remission and to boost the efficacy of cancer vaccines (Hassanpour *et al*., 2018).

Treatment for other diseases: Few researchers have shown that α-Al_2O_3NPs conjugated with vasoactive intestinal peptide have been utilized *in vivo* to treat the allergic asthma against enzymatic degradation of the peptide as anti-asthmatic activity (Hassanpour *et al*., 2018). Another study has indicated that the sol-gel form of Al_2O_3NPs loaded with thrombolytic enzyme streptokinase has shown their sustained liberations of streptokinases with efficient thrombolytic activity as nano-thrombolytic system (Hassanpour *et al*., 2018).

Immunotherapy: Autophagy induction indicates one of the chief targets of immunotherapy and next generation vaccine due to its central role of autophagy for the presentation of antigens to T lymphocytes. In one study, Al_2O_3NPs conjugated with cysteine peptidase A and B have been utilized as *leishmania* vaccine for inducing autophagy in macrophages internalized rapidly by the *leishmania* infected macrophages upon their administration

(Hassanpour *et al*., 2018). Moreover, Al_2O_3NPs have also been used as efficient nano-adjuvant for eliciting systematic and mucosal immunity for anti-HIV vaccine, while Al_2O_3NPs conjugated covalently with a peptomer derived from the C4 domain of HIV-gp120 protein have been utilized to get a potent immunologic efficiency in the mucous (Hassanpour *et al*., 2018).

Toxicity of aluminium oxide nanopartcles: Several studies have focused on the cytotoxicity of the Al_2O_3NPs as they can induce haemolysis in *in vivo* blood samples (Hassanpour *et al*., 2018). Other studies have indicated the neurotoxicity of Al_2O_3NPs as they can interrupt the neuronal rhythmic activities in the antennal lobe of *Drosophila melanogaster* only after 15 min of NPs-administration (Hassanpour *et al*., 2018). A few investigators have indicated that Al_2O_3NPs can reduce the growth rate of environmentally-polluted *Ceriodaphnia dubia* via the induction of oxidative stress (Hassanpour *et al*., 2018). Several other researchers have demonstrated on immunotoxic responses where serum levels of MCP-1 and IL-8 have been increased in mice after exposure of both the long (aspect ratio, 6.2±0.6) and short (aspect ratio, 2.1±0.4) -types Al_2O_3NPs (5 mg/kg), while the enhanced level of IL-1β after the exposure of long-type Al_2O_3NPs (5 mg/kg) (Park *et al*., 2016). In this study, the expressions of CD80, CD86 and CD195 markers have been significantly decreased in spleenocytes of mice exposed with long-type Al_2O_3NPs (5 mg/kg), while the reduced level of CD195 with the dose of 1.25 mg/kg.

Biodistribution and elimination: The biodistribution of the NPs to various organs may vary based on their different shapes, sizes, high surface to volume ratios, charges, surface coatings and different routes of administrations. Few investigators have reported that after single intravenous exposure of Al_2O_3NPs (5 mg/kg), the short type Al_2O_2NPs have been accumulated significantly in the spleen and liver, whereas the long type Al_2O_3NPs in the lung, brain, heart, liver, kidney and spleen at 14 days. It has also been noticed that the accumulated levels have been higher in mice exposed with the long type Al_2O_3NPs in comparison with the short type (Park *et al*., 2016). After administration of Al_2O_3NPs through endocytosis or phagocytosis, metabolism and degradation of the NPs in the biological system or in the phagolysosomal compartment may take place (Mandal, 2018). Larger Al_2O_3NPs (>6 nm) may be accumulated and sequestered in liver and spleen for longer period (Mandal, 2018). The Al_2O_3NPs may be eliminated by intestinal hepatobiliary tract or kidney through passing of feces or urine (<5 nm) (Mandal, 2018).

Conclusions and future perspectives

Antibiotics-resistances acquired by the microorganisms have become a blow to the medical fraternity. Nanomaterials such as Al_2O_3NPs due to their metallic physico-chemical features may be utilized as anti-microbial agents as the microorganisms cannot develop resistance against them. To overcome their bio-toxicity and other biological barriers, and to use them as potent biocompatible drug delivery system, cargos-loaded surface-functionalizations with the attachments of ligands and coatings such as sugars, peptides, proteins, nucleic acids, genes and vesicles are needed to deliver cargos to the targeted site/s of interest towards producing a next-generation bio-nanomaterial for wider biomedical applications. In this regard, more extensive studies regarding their interactions with cells, immunotoxicity, biodistribution, pharmacokinetics and elimination, routes of administration especially oral and intravenous, and effective biological efficacies are required to consider Al_2O_3NPs as potent drug delivery system before going to their translational applications.

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