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Biomedical applications of aluminium oxide nanoparticles

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Aluminium oxide (Al_2O_3) nanoparticles (AlNPs) are class of metal oxide nanoparticles that have diverse biomedical applications owing to their exceptional physicochemical and structural features such as resistance towards wear, chemicals, mechanical stresses as well as their favourable optical properties and a porous vast surface area. Other reasons for widespread applications of AlNPs are their low cost of preparation and easy handling. Therefore, owing to the economic importance, the recent achievements and possible health risks associated with the biomedical applications of AlNPs are overviewed in this work.

1. Introduction: Aluminium oxide nanoparticles (AlNPs), a class of porous nanomaterials, belong to the family of metal oxide nanomaterials; and from the structural point-of-view, they are assembled as corundum-like structure in which six oxygen atoms surround one aluminium atom. Similar to the other metal oxide nanoparticles (NPs), AlNPs can be readily handled and are easily accessible. Also, these cost-effective nanomaterials possess high surface area as well as mechanical strength; and they have exceptional chemical stability towards high temperatures and harsh conditions such as abrasive environment. Further, they possess a low electrical conductivity [1–7]. Moreover, the exceptional optical properties of AlNPs are used as a model for investigation of the properties as well as structural and electronic variations of nanomaterials [4, 8]. In addition, the bioinertness and easy surface functionalisation allows their use in the biological environment [9, 10]. AlNPs can be synthesised using different methods with simple and cost-effective protocols [9]. Their synthesis methods fall into solid phase-based, gas phased-based and liquid-based procedures, ranging from mechanical ball milling, mechnochemical, laser ablation, solution reduction, exploding wire, decomposition and gas evaporation. The detailed protocols for each method have been discussed in detail by Ghorbani [11, 12].

Recent economic analyses show that AlNPs have a rapidly growing market in various industries as well as in the biomedical areas [13], and thus, they have considered as a strategic nanomaterial in the various aspects of life. Regarding the exceptionally useful properties, the availability of various routes for synthesis of the AlNPs and strategic importance of AlNPs, they have been found diverse applications in the human life, particularly in biomedicine and biotechnology (Fig. 1), where they are used in drug delivery (Fig. 2*a*), biosensing (Fig. 2*b*), treatment of diseases (Fig. 2*c*), destruction of microbes (Fig. 2*d*) and biomolecular stabilisation (Fig. 2*e*). Nevertheless, there is no overview in the field. Therefore, herein, we review the main biomedical applications as well as biosafety issues of AlNPs and address the current trends in the field.

2. Biomedical applications

2.1. Drug delivery: AlNPs have been used in the form of ordered mesoporous aluminium oxide for improved oral delivery of anti-blood pressure drug Telmisartan as a poor-water soluble compound. Ordered mesoporous aluminium oxide was synthesised by evaporation induced self-assembly method, and after characterisation by Fourier transform infrared, scanning electron microscopy and X-ray diffraction (XRD), Telmisartan was loaded in its pores using solvent impregnation technique. The results showed a 45% loading efficiency independent of any significant interaction between the drug and the NPs. Also, loading inside ordered mesoporous aluminium oxide resulted in a significant dissolution and release of Telmisartan [14]. In another study, a sol–gel of aluminium oxide–ibuprofen nanocomposite was fabricated to increase the bioavailability of ibuprofen. For this purpose, nano-aluminium oxide was fabricated by controlled hydrolysis of aluminium oxide alkoxide, followed by loading of the as-prepared nano-aluminium oxide particles with the water-insoluble ibuprofen. Then, the prepared nanocomposite was characterised using XRD analysis, UV–Vis spectrophotometry, Brunauer, Emmett and Teller method, Fourier transform Raman spectroscopy and thermogravimetric analysis. As expected, the solubility and controlled release of ibuprofen was significantly increased in the form of sol–gel nanocomposite with aluminium oxide. The mechanism behind this high loading and controlled release efficiency can be attributable to the high surface area, highly porous structure and high density of hydroxyl groups on the surface of the sol–gel nano-aluminium oxide. This study reveals the suitability of this type of nano-aluminium oxide particle as an efficient drug delivery vehicle [15].

Fig. 1 *Biomedical applications of AlNPs*

2.2. Biosensing: Recently, AlNPs have been considered as novel platforms for detection of different molecules. Aluminium oxide, in the form of NPs, has been used to sense bovine serum albumin. To perform the biosensing, the surface of localised surface plasmon resonance (LSPR) sensor was modified with self-assembled anodic aluminium oxide in which an ordered aluminium oxide nanohole structure was formed on a LSPR chip. Based on the obtained results, a diameter of 75 nm and a depth of 0.5 µm of nanohole were found to be the most sensitive sensing layer [16]. In another study, core/shell nanocarbon-modified aluminium oxide nanocrystal was used to sense DNA in a competitive bioassay. This carbon layer allowed easy surface engineering, and it also was used as a platform to increase the stability, biocompatibility and surface reactivity of the aluminium oxide nanocrystals. For biosensing applications, the florescent nature of the aluminium oxide nanostructures was applied in different biodetection purposes such as cell imaging, intracellular cargo monitoring and in vitro DNA detection [17]. In addition to biomolecule detection, AlNPs have been shown capability to sense chemicals. In alignment with this application, the aluminium oxides NPs have been used as a nanocomposite with chitosan to detect phenolic molecules. AlNPs were decorated on a chitosan film and then horseradish peroxidase (HRP) was loaded on the fabricated nanocomposite. Afterwards, the HRP-loaded nanoelectrode was used to amperometrically detect hydroquinone with a detection limit of 1 nm and dynamic range of 5×10^{-9}–7×10^{-5} M in ~5 s [18].

2.3. Cancer therapy: The aluminium oxide nanomaterial in the form of nanotubes containing Thapsigarin, which were fabricated using a modified pulse anodisation process and then loaded with Thapsigarin, was co-administered with an autophagy inhibitor, namely 3-methyladenine, to target autophagy signalling in both cancerous and normal human cells. In normal cells, the Thapsigarin-loaded aluminium oxide nanotube did not show any cytotoxic effect, while it induced autophagy signalling in the cancer cells, indicating the capability of aluminium oxide nanotubes as new generation of drug delivery vehicle for anti-cancer therapy [19]. In addition to the suitability of aluminium oxide nanotubes in cancer therapy, the anti-cancer properties of spherical nano-aluminium oxide particles have been reported. In a study by Rajan Y.C. *et al*., a poly-glutamic acid modified AlNPs was fabricated and applied as cytotoxic agents to induce cell death in human prostate cancer cells. Upon treatment

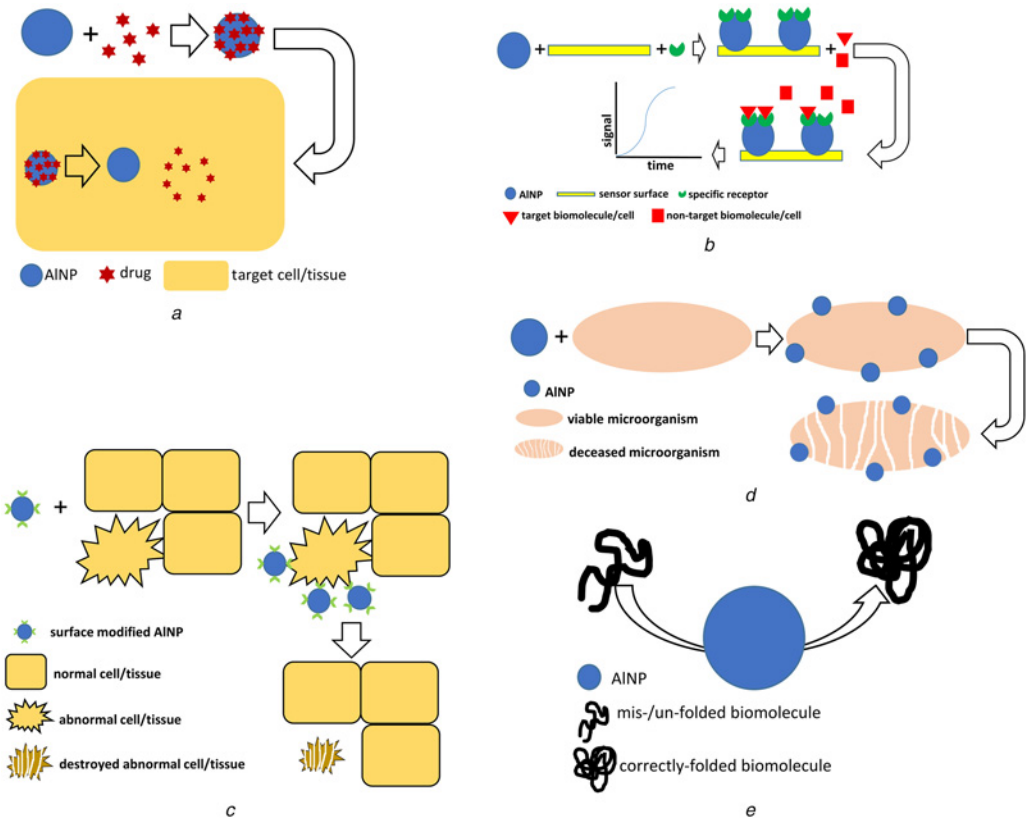

Fig. 2 *Main applications of AlNPs in different biosystems*
a Application of AlNPs in drug delivery systems
b Biosensing using AlNPs
c Therapeutic application of AlNPs
d Anti-microbial effect of AlNPs
e Role of AlNPs in folding of biomolecules

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of PC-3 prostate cancer cells, AlNPs showed cell cytotoxicity towards them through induction of reactive oxygen species and subsequent mitochondrial dysfunction [9]. A different study reports that the nanopetal AlNPs-treated mouse neuroblastoma Neuro-2a cells showed decreased viability and increased surface zeta-potential towards negative values. The percentage of cell viability and the value of zeta potential were shown to be related to the shape of aluminium oxide nanostructures used. Among the petal, plate and wedge-like nano-aluminium oxide, the nanopetal aluminium oxide showed the highest level of cell cytotoxicity, followed by the nanoplates and wedge-like NPs. Also, the highest change in the zeta potential of cell surface has been observed for AlNPs [20]. As an advanced strategy for cancer treatment, AlNPs have been applied as efficient adjuvant in cancer immunotherapy in vitro and in vivo. In this strategy, AlNPs were used as a cancer antigen carrier to autophagosomes of dendritic cells, by which the delivered antigens were effectively presented to T-cells. Application of AlNPs resulted in a significant increase in the number of activated T-cells that in turn led to eliciting a potent anti-tumour activity of these cells and a considerable cancer remission. This study proves AlNPs as potential candidate for boosting the efficacy of cancer vaccines [21].

2.4. Anti-microbial effects: Owing to the large surface area of AlNPs, they show strong anti-microbial activities. In accordance with this finding, the anti-*Escherichia coli* (*E. coli*) property of AlNPs has been proved in a study by Sadiq M. *et al.*, in which 179 nm sized-AlNPs of various concentrations were incubated with bacterium *E. coli*. A mild anti-growth effect has been observed, which was due to the electrostatic interaction between the NPs and bacterial cells. Also, a small decrease was reported in extracellular protein content of the bacterium [2]. In a similar study, AlNPs showed anti-growth effects of 57% on *Bacillus subtilis*, 36% on *E.coli* and 70% on *Pseudomonas fluorescens*, which was originated from direct attachment of the NPs to cell walls of these bacteria [6]. In addition to the application in the form of pure NPs, aluminium oxide nanomaterials have been shown potential antimicrobial properties against *E.coli* and *Staphylococcus epidermidis* (*S.epidermidis*) when used in the form of aluminium oxide–silver nanocomposite, indicating the potential biomedical applications of nano-aluminium oxide as composite structures [7]. In another study, aluminium oxide nano-coatings, in the form of Fe_3O_4/aluminium oxide core/shell magnetic NPs, showed an incredibly magnetically-derived photothermal killing effects on a range of gram-negative, gram-positive and drug-resistant bacterial isolates. In this intelligently designed nanocomposite, aluminium oxide shell functions as recogniser of bacterial cells that subsequently are killed photothermally through the Fe_3O_4 core. Also, the core Fe_3O_4 could be used to guide the NPs towards the bacterial cells by using magnetic field [22].

2.5. Treatment of other diseases: Alpha-AlNPs were conjugated with vasoactive intestinal peptide and used as anti-asthmatic nano-drug to treat the allergic asthma in mouse model, where alpha-AlNPs were used for protection of vasoactive intestinal peptide against enzymatic degradation in the lung of asthmatic mouse model, and showed a strong anti-asthmatic activity compared with the non-conjugated vasoactive intestinal peptide and beclomethasone [23]. The potential benefit of AlNPs has been demonstrated as nano-thrombolytic system. To showcase this potential, the thrombolytic enzyme streptokinase was loaded in a sol–gel form of AlNPs. The prepared streptokinase-AlNPs showed a sustained release of streptokinase and an efficient thrombolytic activity on different samples, when their size was below 500 nm [24].

2.6. Bimolecular preservation and stabilisation: Based on the results of a study by Volodina V.K. *et al*, AlNPs could serve as a nanoplatform for correct folding of protein molecules. To be used as an renaturing material, AlNPs interact electrostatically with denatured negatively charged proteins, and prevent their aggregation and mis-folding. In other words upon addition to the reaction, AlNPs keep the refolding process under control until correct folding of the mis-/un-folded protein [25].

2.7. Immunotherapy: Autophagy induction remains as one of the main targets of immunotherapy and next-generation vaccines, owing to the central role of autophagy in presentation of antigens to T lymphocytes. For this reason, the potential of AlNPs has been studied as autophagy inducer. In one study, cysteine peptidase A and B were conjugated to AlNPs and used as *leishmania* vaccine to induce autophagy in macrophages. The conjugated NPs were shown to be rapidly internalised by the *leishmania*-infected macrophages upon administration of these NPs [26]. In addition to autophagy induction, the AlNPs have been proved as efficient nano-adjuvants to elicit systematic and mucosal immunity towards potential use for designing an anti-HIV vaccine. Accordingly, a peptomer derived from the C_4 domain of HIV-gp120 protein was conjugated covalently onto AlNPs, which resulted in a 300 nm nano-conjugate that was capable to elicit a strong immunologic reaction in the mucus [27].

3. Advantages and limitations

3.1. Beneficial features: A number of features make AlNPs attractive nanomaterials [1–10]:

(i) These nanomaterials are readily available through established synthesis methods.

(ii) Their vast surface area allows for readily conjugation with other molecules of various origins such as chemical and biological molecules.

(iii) They can easily interact with the biological interfaces that allow for using them for biological purposes.

(iv) They are stable enough to be used in the various conditions, especially in the harsh non-biological environments.

(v) The protocols for their surface functionalisation are straight forward, which makes them ideal nanomaterials for development of a vast type of nanobiomaterials.

3.2. Limitation: In spite of wide-spread biomedical applications, aluminium oxide nanomaterials demonstrated environmental biotoxicity. Therefore, several studies have focused on the evaluation of cytotoxicity of these nanomaterials on various organisms. The results of a study by Vinardell P.M. *et al.* showed that AlNPs can lyse erythrocyte as compared to macro-sized aluminium oxide in human, rat and rabbit blood samples. The nanopowder induced a more intense haemolysis in these samples, demonstrating the risk of blood contamination by AlNPs as potent lysing nanomaterials [28]. The neurotoxicity of AlNPs has been shown in *Drosophila melanogaster* in which AlNPs could interrupt the neuronal rhythmic activities in the antennal lobe. An important finding was that the neurotoxicity of AlNPs has been appeared only after 15 min of administration [29]. In order to environmentally monitor aluminium oxide nanomaterials contamination a freshwater aquatic invertebrate – *Ceriodaphnia dubia* – has been introduced as a potential bio-indicator. In this approach, the level of water contamination by AlNP was correlated directly to the cytotoxicity observed on

Table 1 Biomedical application of AlNPs

Applications	Description
drug delivery	telmisartan [14] and ibuprofen [15]
biosensing	bovine serum albumin [16], DNA in a competitive bioassay [17], hydroquinone [18]
cancer therapy	anti-cancer therapy [19], cytotoxic agents to induce cell death in human prostate cancer cells [9], changing the zeta potential of cell surface [20], boosting the efficacy of cancer vaccines [21]
anti-microbial effects	strong anti-microbial activities [2], potential antimicrobial properties against *E. coli* and *S. epidermidis* [7], photothermal killing effects [22]
treatment of other diseases	anti-asthmatic [23], as nano-thrombolytic system [24]
bimolecular preservation	as nanoplatform for correct refolding of mis-/un-folded protein molecules [25]
immunotherapy	as leishmania vaccine to induce autophagy in macrophages [26], as potent vaccination adjuvant [27]

Ceriodaphnia dubia, which was inferred from the bioavailability of the NPs inside this organism. Mechanistically, AlNPs can decrease the growth rate of *Ceriodaphnia dubia* through induction of oxidative stress (Table 1) [30].

4. Conclusion and future perspectives: Considering the needs of rapidly growing biomedical science for using new class of materials, AlNPs have been considered as suitable nanomaterials which have been found to be applicable in different aspects of biomedical science and biotechnology. Nonetheless, some observed biotoxicity may hinder the rapid advancement of AlNPs towards more applications, for instance their use as vehicles for intracellular delivery of therapeutic nucleic acids and proteins. Therefore, it seems that using some surface engineering strategies is inevitable strategy to produce completely biocompatible AlNPs towards producing a next-generation bionanomaterial with wider biomedical uses. Therefore, due to attractive features, the future research of AlNPs would be exciting as other areas of biomedical science are being developed. In other words, these nanomaterials can be applied in other less-investigated areas such as in vivo imaging, nucleic acid delivery, targeted therapy and tissue engineering. Synthesis of different forms of AlNPs, e.g. other shapes, would expedite the future research on their application. Also, with the help of other disciplines such as nanoscale surface chemistry, AlNPs can be used as artificial enzymes for developing novel diagnostic assays.

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