A Review on Toxicity and Challenges in Transferability of Surface-functionalized Metallic Nanoparticles from Animal Models to Humans

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Abstract
The unique size and surface morphology of nanoparticles (NPs) have substantially influenced all aspects of human life, making nanotechnology a novel and promising field for various applications in biomedical sciences. Metallic NPs have gained immense interest over the last few decades due to their promising optical, electrical, and biological properties. However, the aggregation and the toxic nature of these NPs have restricted their utilization in more optimized applications. The optimum selection of biopolymers and biological macromolecules for surface functionalization of metallic NPs will significantly improve their biological applicability and biocompatibility. The present mini-review attempts to stress the overview of recent strategies involved in surface functionalization of metallic NPs, their specific biomedical applications, and comparison of their in vitro, ex vivo, and in vivo toxicities with non-functionalized metallic NPs. In addition, this review also discusses the various challenges for metallic NPs to undergo human clinical trials.

Keywords
Biomedical applications, comparative toxicity, human clinical trials, metallic nanoparticles, nanotechnology, surface functionalization.

Nanotechnology
The term nanotechnology was first introduced in 1959 by an American scientist, Dr. Richard Feynman, in his physics lecture and stated that “There’s plenty of room at the bottom.” He floated an idea in the mind of other scientists on research on the atomic level for new development in the field of science and technology. Because of the unique characteristics attributed to the surface morphology and size distribution of nanoparticles (NPs), scientists from different fields have focused on nanotechnology. From 2017 to 2019, the industrial market value of nanoscience and nanotechnology was found in the range of 2 to 3 billion dollars. However, the average compound annual growth rate is increasing to 29.5% from 2017 through 2021, which could be used as basis to predict that the industrial market value of nanoscience and nanotechnology might reach 7.3 billion dollars in 2023 [1]. The size of NPs is found in the range of 1–100 nm, and it can be classified into four different dimensions, i.e., zero dimension, one dimension, two dimensions, or three dimensions [2]. The acceptance of nanomaterials is highly appreciable, due to their size variability, excellent dispensable properties, high mobility, and specific mechanical, magnetic, and optical strength, which make them different from the microscopic-range materials [3, 4].

The utilization of nanotechnology has been found in numerous fields of science and technology such as biological and biomedical sciences, bioengineering, environmental remediation fields, material technology, and food and agriculture sciences [5, 6]. It is used in in vitro, ex vivo, and in vivo applications as antibacterial and antifungal agents, fluorescent labels, antimicrobial agents, transfection labels, cell imaging, drug delivery, biosensors, electrochemical devices, and energy storage diagnostic and therapeutic agents [7, 8].

The field of nanotechnology is also increasing our daily life expectancy by providing new opportunities to control different imaginable diseases. Different types
of metallic NPs, particularly gold, silver, platinum, and zinc NPs are extensively used in different sectors of the food and pharmaceutical industries. Metallic NPs have excellent and unique physicochemical properties such as good chemical stability, high thermal stability, optical properties, electronic properties, remarkable photocatalytic activity, and low cost [9]. They can be surface-functionalized or coated with other biomolecules or biopolymers to create biocompatible and unique NPs with desired properties. Due to these unique physicochemical characteristics of these metallic NPs, they could have several biomedical applications, including drug delivery, protein purification, bacterial detection, contamination decoloration, enzyme immobilization, hyperthermia, and many others [10]. At present, these metallic NPs are also used in toothpaste, coatings of sanitary ware, sunscreens, water cleaning, and food/feed and cosmetic products that are all directly in contact with the skin of humans and animals [11, 12].

This review is presented in three sections. The first section highlights the importance of nanotechnology and its applications in biomedical fields; the second section describes the low toxicity of surface-functionalized metallic NPs over non-modified metallic NPs. The last section of this review focuses on the challenges in transferability of surface-functionalized NPs from animal models to humans.

Surface functionalization of metallic NPs

Bio-functionalized metallic NPs are highly versatile nano-structured materials that have enormous potentials to be utilized in various applications such as bio-imaging, optoelectronics, biosensing, photonics, and nanomedicine. Several physicochemical and biological advantages have been reported for surface-modified metallic NPs (Figure 1).

Besides surface functionalization of metallic NPs with different biological molecules, polymers or drugs can modify their bio-distribution and toxicity profile substantially in the case of targeted drug delivery to the mononuclear phagocyte system (MPS) such as in the lungs, bone marrow, liver, and spleen. Whenever NPs are administered intravenously, the host immune system can recognize them and rapidly eliminate them from the general circulation by phagocytes [15]. Apart from NP size, the hydrophobicity of the synthesized NPs determines the blood components level that binds this surface (e.g., opsonins). Hence, surface hydrophobicity influences the in vivo fate of NPs [16]. Indeed, conventional NPs are rapidly opsonized and eliminated by the MPS [17]. To increase the chances of the desired therapeutic outcomes in targeted drug delivery systems, the opsonization and elimination rate of in vivo circulatory NPs should be minimized. This can be efficiently achieved by surface functionalization of metallic NPs with hydrophilic biodegradable polymers (e.g., polyethylene oxide, poloxamine, polyethylene glycol [PEG], chitosan, carboxymethyl cellulose, polysorbate 80, and polyoxamer), biomolecules (e.g., proteins, peptides, antibodies), drugs, or different biopolymers used in combination as hybrid (Figure 2).

In general, metal-cored NPs stabilized with hydrophobic ligand such as gold, quantum dots, and iron oxide are easily entrapped in a PEG derivative’s micellar shell of lipids–PEG. The bulky PEG molecule prevents plasma proteins adsorption and uptake by the macrophages by acting as a steric barrier, resulting in longer-time body circulation NPs with improved overall bio-distribution and biocompatibility [18]. Although surface-functionalized polymeric NPs can be synthesized readily in a consistent manner with respects to their size and chemical composition in comparison with any other NP system, they are subject to clearance through reticuloendothelial system [19]. Therefore, several new strategies for designing surface functionalization of polymeric NPs in order to enhance overall biodistribution and biocompatibility are reported. PEGylation is perhaps the most commonly used method for the improvement of bio-distribution and biocompatibility by surface modification of polymeric nanocapsule [20]. Few studies have been reported on the preparation of targeted NPs using PEGylation techniques that include functional PEG chains, specifically the preparation of poly(ecaprolactone)-PEG and poly(lactic-acid)-PEG copolymers with biotinylated end groups. Other systems use PLA-PEG-maleimide copolymers to synthesize NPs that can be bound to thiol-containing targeting agents. However, it is usually necessary to add cysteines to increase the possibility of reducing their activity. However, PEG addition for surface functionalization of polymeric nanocapsule has some limitations. For example, disparities can occur in surface densities when larger-size synthetic molecules are attached to particle surface, creating an uneven distribution of targeting moieties. Furthermore, low-molecular-weight PEG destroys or modifies the structure of NPs systems in body tissues due...
to its water-soluble properties, which hinders the targeting of target-specific delivery system [21]. PEG also provides substantial benefits, such as reduced antigenicity and immunogenicity of the drug after surface functionalization with NPs.

Their synthesis is very simple, which, coupled with their desirable physicochemical and biological characteristics, appreciable biocompatibility, and low in vivo toxicity, makes these functionalized NPs highly attractive for researchers for the aforementioned applications. The functionalization of biological macromolecules and biopolymers with different types of nanomaterials in a controlled way enhances greater activity and has a tremendous biological application in pharmaceutical sciences such as biosensing, imaging, and various chronic diseases treatment [24, 25]. A wide variety of organic molecules with different sizes, compositions, and complexity are present in nature, which gives function and structure for the different biological processes. Small molecules, such as vitamins, lipids, sugar, and peptides, and larger molecules, such as DNA, RNA, proteins, and enzymes, are examples of organic molecules that are used for various biological processes.

In addition, the functionalization of biopolymers on NPs surfaces reduced the opsonization of NPs by different complement and other serum factors [26]. However, the structural and intermediate configurations of different biopolymers can also alter the biological properties of polymeric NPs. For instance, brush-like PEG molecules reduced the complement activation and phagocytosis, whereas PEG molecules with mushroom-like surface favored phagocytosis and also potent complement activators [27]. At present, nanoscale effects and interaction mechanisms between metallic NPs and bio-macromolecules have not been well studied or understood. Ruckenstein et al. reported that although many metallic NPs possess excellent physicochemical properties, they do not have appropriate properties for surface functionalization applied for specific applications [28]. Hence, surface functionalization of NPs must be done in a controlled manner with conjugated molecules that change the structure, morphology, and surface while maintaining the overall mechanical integrity of metals.

### Biomedical applications of surface-functionalized metallic NPs

Several applications of metallic NPs in the field of science and technology, especially in biomedical science, are an emerging area of applied research. The physicochemical and optical properties of metallic NPs were susceptible to surface functionalization, thereby suggesting potential candidates in the detection and biomedical applications. Few of the recently reported surface-functionalized metallic NPs are listed in Table 1 with their biomedical applications.

Further, the highly significant antimicrobial effects of surface-functionalized metallic NPs, suggest the utilization of nanoconjugates as novel antibacterial agents [44]. The surface-functionalized metallic NPs have been reported to have improved intracellular uptake and biocompatibility for drug delivery [45]. At present, cancer is the most prominent factor of mortality and morbidity globally. More than 90 million people suffer from different types of cancer, and the number is continually increasing despite the numerous therapeutic efforts [46]. Because of the plasmonic and unique surface-mobilized nature of functionalized metallic NPs, they are useful for highly specific targeting and imaging of cell surface or specific site of actions for applications in cancer therapies [47]. The labeling of biomolecules with NPs has improved the visualization of cellular components in vivo using electron microscopy [48]. An investigation used polyvinyl alcohol–functionalized silver NPs for detecting labeled DNA for breast cancer gene [49]. In the last few decades,
viruses, including HIV, Zika virus, influenza virus, and many others, have become a serious concern globally because of their potential to cause pandemics. In a study, dose-dependent surface-modified NPs were markedly attached to the surface of HIV, thereby inhibiting the binding of the virus to host cells [50]. The metallic NPs coated with biocompatible nanoconjugates readily bind to the living cells surface while maintaining the morphology of normal cells, i.e., neurite extensions [51]. After tissue injuries, the healing process is a complex physiological process with overlapping phases of tissue inflammation and remodeling, the rate of which is substantially affected by the size, depth, and especially the type of the injury as well as bacterial infections [52]. Several polymeric functionalized metallic NPs with highly significant wound healing properties have been reported [53, 54]. Another study has also observed that biopolymer-functionalyzed metallic NPs enhanced the stability of nanocomposite in aqueous dispersion, which is substantially more important for thin film deposition or for use as imaging probes [55].

Toxicity of functionalized metallic NPs versus non-functionalized metallic NPs

Although the use of metallic NPs has gained much attention in industrial and biomedical sciences, several reports have also been mentioned their toxicity and adverse effects on the cellular components and sometimes on the overall biological systems [56, 57]. Currently, NPs have been studied for cell toxicity, genotoxicity, and immunotoxicity. The cytotoxicity of metallic NPs is generally associated with the comfortable oxidation of metallic ions, which are relatively toxic for cellular components. Since they have a greater surface area and higher chemical reactivity, it results in increased production of reactive oxygen species [58]. There are several other suggested mechanisms for metallic NPs cytotoxicity, such as contamination with the toxic elements, physicochemical properties, high surface charge, fibrous structure, and generation of radical species [59, 60]. Many researchers have agreed that NPs interfere with the detection systems or with assay materials. It addition, it has been reported that metallic NPs produced size-dependent toxicity, as silver NPs with a diameter of 10 nm showed greater tendency to penetrate into the cellular systems of living beings in comparisons with silver NPs with greater diameters (i.e., 20–100 nm) [61]. Similarly, NPs show variability in their toxicity levels at different aspect ratios depending on their shape and dimensions. For example, 10-μm asbestos fibers with a three-dimensional structure cause lung cancer, whereas shorter asbestos fibers with a two-dimensional structure cause mesothelioma; meanwhile, 2-μm fibers with one dimension cause asbestosis [10]. Typically, NP toxicities also increase with greater surface area particle. It can also be observed that NPs with the same dose react with human cells in different manners [62].

Hence, because of the reported toxic effects of metallic NPs, researchers continuously modify the dose, size, shape, surface morphology, and other properties of metallic NPs that can cause in vitro or in vivo toxicities through surface functionalization of metallic NPs using different types of bio-polymers, biomolecules, and other non-toxic conjugated systems. These physicochemical factors of metallic NPs are exceptionally important for their toxicological profile, bio-distribution, accumulation inside body tissues, metabolism, and elimination [63]. Many researchers have reported the toxicity profile of metallic NPs after surface functionalization using different conjugated materials for various applications (Table 2). The results of these studies indicated that the toxicity of various metallic NPs has been reduced after functionalization with different biological molecules, biopolymers, and drugs.

According to the results of previous studies, orally administered polymeric-coated silver NPs (chitosan and polyethylene glycol) produced low systemic toxic effects; meanwhile, compared with silver NP alone at the same dose, i.e., 90 μg/kg, polymeric-coated silver NPs showed no local toxic effects (Figure 3).

Furthermore, significantly lower rates of hemolysis were observed when gold NPs functionalized with gum karaya

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**Table 1** Surface-functionalized Metallic Nanoparticles with Their Applications

<table>
<thead>
<tr>
<th>S. no</th>
<th>NPs</th>
<th>Conjugated with</th>
<th>Size and shape</th>
<th>Application</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Silver</td>
<td>Chitosan+alginate</td>
<td>50–70 nm; round</td>
<td>Anti-bacterial</td>
<td>[29]</td>
</tr>
<tr>
<td>2</td>
<td>Silver</td>
<td>Chitosan</td>
<td>30–40 nm; spherical</td>
<td>Anti-bacterial, anti-coagulant</td>
<td>[30]</td>
</tr>
<tr>
<td>3</td>
<td>Silver</td>
<td>Catechol+chitosan</td>
<td>40–70 nm; quasi-shaped</td>
<td>Anti-bacterial</td>
<td>[31]</td>
</tr>
<tr>
<td>4</td>
<td>Silver</td>
<td>Chitosan+antibiotics</td>
<td>80–120 nm; quasi-shaped</td>
<td>Anti-bacterial</td>
<td>[32]</td>
</tr>
<tr>
<td>5</td>
<td>Gold</td>
<td>Poly-lactic acid-poly-ethylene glycol</td>
<td>216 nm; lamellar structure</td>
<td>Anti-inflammatory</td>
<td>[33]</td>
</tr>
<tr>
<td>6</td>
<td>Silver</td>
<td>Glycolic acid</td>
<td>30–40 nm; spherical</td>
<td>Treatment of skin cancer cells</td>
<td>[34]</td>
</tr>
<tr>
<td>7</td>
<td>Silver</td>
<td>Polylvinyldiiodolone+antibiotics</td>
<td>60–70 nm; quasi shaped</td>
<td>Anti-bacterial</td>
<td>[35]</td>
</tr>
<tr>
<td>8</td>
<td>Gold</td>
<td>Hyaluronic acid</td>
<td>14–19 nm; spherical</td>
<td>Hyaluronidase inhibitor</td>
<td>[36]</td>
</tr>
<tr>
<td>9</td>
<td>Silver</td>
<td>Xylase</td>
<td>20–35 nm; spherical</td>
<td>Detection of mercury level in blood</td>
<td>[37]</td>
</tr>
<tr>
<td>10</td>
<td>Silver</td>
<td>Dextran</td>
<td>10–14 nm; spherical</td>
<td>Detection of insulin level in blood</td>
<td>[38]</td>
</tr>
<tr>
<td>11</td>
<td>Silver</td>
<td>Guar gum</td>
<td>6–10 nm; spherical</td>
<td>Detection of ammonia level in blood</td>
<td>[39]</td>
</tr>
<tr>
<td>12</td>
<td>Iron</td>
<td>β-Cyclodextrin-dextran-g-stearic acid</td>
<td>60–100 nm; micelles</td>
<td>Cancer cells imaging</td>
<td>[40]</td>
</tr>
<tr>
<td>13</td>
<td>Gold</td>
<td>Cellobiose</td>
<td>12–35 nm; spherical</td>
<td>Measurement of activity</td>
<td>[41]</td>
</tr>
<tr>
<td>14</td>
<td>Gold</td>
<td>Antibodies</td>
<td>30–58 nm; spherical</td>
<td>Treatment of pancreatic carcinoma</td>
<td>[42]</td>
</tr>
<tr>
<td>15</td>
<td>Silver</td>
<td>Heparin</td>
<td>60–90 nm; spherical</td>
<td>Anti-angiogenesis</td>
<td>[43]</td>
</tr>
</tbody>
</table>

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**Table 2** Toxicity of Surface-Functionalized Metallic Nanoparticles

<table>
<thead>
<tr>
<th>NPs</th>
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</tr>
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<tr>
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</tr>
<tr>
<td>Silver</td>
<td>Glycolic acid</td>
<td>30–40 nm; spherical</td>
<td>Treatment of skin cancer cells</td>
</tr>
<tr>
<td>Silver</td>
<td>Polylvinyldiiodolone+antibiotics</td>
<td>60–70 nm; quasi shaped</td>
<td>Anti-bacterial</td>
</tr>
<tr>
<td>Gold</td>
<td>Hyaluronic acid</td>
<td>14–19 nm; spherical</td>
<td>Hyaluronidase inhibitor</td>
</tr>
<tr>
<td>Silver</td>
<td>Xylase</td>
<td>20–35 nm; spherical</td>
<td>Detection of mercury level in blood</td>
</tr>
<tr>
<td>Silver</td>
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</table>
and xanthan gum were used, compared with using gold NPs alone at concentrations of 200 μg/mL [78, 79]. Metallic NPs functionalized with porphyrin and pectin produced no significant effect in kidney cells, even at higher concentrations, i.e., 100 μM [80, 81]. Additionally, a significantly higher percentage of macrophage cell viability was found after exposure to polymeric functionalized metallic NPs than the metallic NPs themselves [82]. A previous report clarified that metallic NPs with smaller diameter (10 nm) tend to penetrate the biological membrane and produce more toxic effects at the deepest layers of the stratum corneum; meanwhile, no local toxicity was reported for polymeric functionalized metallic NPs [83]. The findings of the oral toxicity study on rats model also demonstrated that gellan gum–functionalized NPs had limited effects on the biochemical and hematological indexes at a dose of 1500 ppm [84]. Identical findings were also observed in an in vivo toxicity study in a zebrafish model [85]. Worthington et al. observed that the human alveolar epithelial cell viability was significantly much higher after inhalation of chitosan-coated copper NPs in comparison with exposure of non-functionalized copper NPs [86]. Similarly, citrate-coated gold NPs showed no toxicity on embryonal fibroblasts in the MTT assay up to the maximum concentration; however, such high concentrations of non-functionalized gold NPs induced significant changes in cell morphology [87]. Furthermore, quantum dots showed no cytotoxicity on fibroblasts using impedance microscopy [88]. Chitosan-coated silver NPs produced minimum hepatic cellular changes, and with therapeutic concentration, no changes were found in the heart, kidney, or liver tissues of rats (Figure 4) [32]. Hence, based on available toxicity data and their experimental models, it may be concluded that several metallic NPs are more valuable and less toxic to biological systems after surface functionalization with different conjugated systems principally with bio-polymers.

### Challenges in transferability of surface-functionalized NPs from animals models to humans

Despite several potential advantages of surface-functionalized NPs, the utilization of these unique NPs systems for tissue targeting in human body system has not been widely embraced in comparison with other classes of medicines, including antibody fragments, liposomal systems, and many others. Currently, all surface-modified NPs are at the preclinical or initial discovery stage. The reason behind the above phenomenon is slightly complex and needs to be explored. Animal models are generally used for the evaluation of potential pharmacological activities in nanomaterial prior to human clinical trials. Even various animals testing are needed prior to human exposure [89]. However, the transfer of animal testing to human trials has several restrictions and challenges. Müller et al. interpreted the challenges as being “lost in translation” [90]. At present, drug candidates testing
are commonly reported on mouse models studies prior to clinical trials. However, it is already established that certain biological responses in rodent models are not transferable to or comparable with larger animals and human clinical trials [89]. Concerning the biomedical applications of nanocarriers as drug delivery systems, the behavior assessment in biological fluids is the most critical prior to the evaluation of the pharmacological effect [91]. Most NP systems are formulated to be administered intravenously; thus, their first exposure is the blood plasma with biological material; then, NPs systems will cover with biological macromolecules or physically adsorbed proteins [92]. This new complex produced undesirable responses such as nanocarrier aggregation and rapid clearance from the blood stream, accumulation in specific tissues due to unspecific cell uptakes, and inflammatory responses of the body [93]. The physicochemical properties of nanomaterial, including their shape, size, charge, hydrophilicity, and, more importantly, surface functionalization, affect the formation of this complex [91]. Therefore, there is an urgent need to understand and modify these physicochemical properties during the formation of nanomaterials for clinical applications. Importantly, surface functionalization of NPs systems was found to significantly influence cellular uptake in biological systems [94]. In reported literatures, a significant connection between NP aggregation in biological fluid and in vivo bio-distribution [95, 96]. Therefore, based on the above circumstances, we suggest that surface-functionalized NPs should be first evaluated in animal model using plasma cell line type to ensure the safe transferability of this unique drug delivery systems from animal trials to in vivo human experiments. Additionally, the same animal trials, at least in vitro tests and blood plasma studies, should also be carried out with human cell lines and these obtained outcomes should be compared in the respective animal studies. This could provide possible predictions on whether the stability of NPs in the blood is the same in human systems. Ideally, this is the most suitable way for the smooth transfer of surface-functionalized NPs from animal models to human clinical trials.

**Conclusions and future perspectives**

As research on metallic NPs has exponentially increased, appropriate awareness of multifunctional hosts for surface functionalization of metallic NPs has increased in scientific fields. Using different bio-polymers, bio-molecules, and many other biological macromolecules exhibited enormous potential for the surface functionalization of metallic NPs owing to their advantages such as low toxicity, biocompatibility, and high target site selectivity. This mini-review creates a comprehensive insight into the approaches and efforts applied for surface functionalization of metallic NPs. According to the reported literature, surface-modified metallic NPs have been proven to have low toxicity and high intracellular uptake for drug delivery. There is significant space available for the exploration of effective surface functionalization and coupling with metallic NPs to produce a stable, bioactive, and highly biocompatible interface. Considering the applications of metallic NPs in various biomedical fields, there is a substantial need for new Food and Administration approval that is free of bias for in vivo pharmacological and
toxicological models for surface-functionalized metallic NPs studies. It is hoped that this mini-review would help provide current knowledge regarding the recent progress and toxicity of surface-functionalized metallic NPs and thus lead to more nano-conjugated systems with low toxicity that can be applied for drug delivery and treatment of various diseases.

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