

Toxicity Challenges of Metal Nanoparticles in Zoonotic Disease Treatment: Strategies and Innovations

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Abstract

Metal nanoparticles (MNPs) have garnered significant attention for their potential application as a novel means of combating zoonotic diseases. MNPs are unique, not only due to their small size but also their high surface-to-volume ratio and their potent antimicrobial properties. Despite the challenges posed by parasitic zoonotic diseases that are transmitted from animals to people, their effective treatment remains a serious public health concern. Although MNPs have been shown to have some potential advantages, several challenges are associated with their use, including cytotoxicity, bioaccumulation, adverse immune reactions, and unanticipated, possibly harmful side effects that may adversely affect health. The purpose of this review article is to examine the challenges associated with the toxicity and side effects of MNPs in the treatment of parasitic zoonotic diseases, as well as potential strategies that can be adopted to minimize these impacts. Recent studies in this area have focused on optimizing nanoparticle design and surface modification, utilizing biocompatible coatings, reducing therapeutic doses, and developing targeted drug delivery systems, thereby maximizing efficiency and accelerating the delivery of drug. Several solutions have been proposed in this regard, including the surface engineering of nanoparticles with biocompatible coatings, nanoliposomes, and magnetic nanoparticles designed to deliver drugs specifically, as well as innovative technologies that can help control the release of drugs. Furthermore, it is possible to develop toxicity prediction models using artificial intelligence and bioinformatic analyses to help identify risks arising from the use of nanoparticles more accurately.

1. Introduction

The problem of parasitic zoonotic diseases has always captured the attention of researchers due to the widespread implications that they have on public health and the global economy [1]. During the last few years, numerous studies have investigated the use of Metal nanoparticles (MNPs) in diagnosing and treating parasitic zoonotic diseases using this novel approach [2, 3]. The unique physical and chemical properties of MNPs make them a promising candidate for treating these diseases, as they possess a small size, a high surface-to-volume ratio, and the ability to combat pathogens (Table 1) [4-6].

Despite this, several challenges come with the use of nanoparticles [7]. A significant challenge with MNPs is that they could be toxic to both human and environmental cells. The side effects of some MNPs have been shown in studies to be damaging to DNA, causing oxidative stress, and triggering inflammation [8]. Additionally, the bioaccumulation of nanoparticles in several body organs, including the liver and kidneys, has raised concerns about the health consequences of MNPs. Moreover, adverse immune reactions can also be a significant and important issue when using MNPs, reducing therapeutic efficacy and increasing risks [9].

Using MNPs in the treatment of zoonotic diseases, including their toxicity and side effects, presents several challenges. This review examines these challenges closely and develops novel strategies to reduce MNP risks. Furthermore, new technologies, including nanoliposomal systems and nanomaterials, can be explored in the context of targeted drug delivery. These technologies can improve the safety and efficacy of MNPs.

2. Parasitic Zoonotic Diseases and Nanotechnology

Zoonotic parasitic diseases are infections that are naturally transmissible between vertebrates and humans, and are caused by a wide range of parasites, including protozoa, helminths, and arthropods, and are considered a significant threat to public health and livestock [10, 11]. Prominent examples of these diseases include leishmaniasis [12], toxoplasmosis [13], hydatid cysts [14], and trypanosomiasis [15]. The importance of these diseases is not only due to their direct impact on human and animal health, but also due to the economic consequences resulting from reduced livestock productivity, treatment costs, and disease control [16]. Climate change, urbanization, and increased contact between humans and animals have heightened the risk of disease transmission. Therefore, understanding ways to prevent, early detect, and effectively treat zoonotic parasitic diseases is essential to reduce their global burden.

Nanotechnology, as an advanced technology, has brought about significant developments in various fields, including medicine, drug delivery, and disease diagnosis [17-19]. Nanoparticles, due to their small size and high specific surface area, enable the precise targeting of diseased cells and the controlled release of drugs in target tissues, thereby reducing the side effects of traditional treatments [20-22]. Additionally, nanobiosensors facilitate rapid and sensitive disease diagnosis in their early stages, while nanomaterials in tissue engineering aid in regenerating damaged organs and tissues [23]. In addition, nanotechnology plays a crucial role in the development of vaccines, medical imaging, and the fight against antibiotic-resistant pathogens [24].

Metallic nanoparticles have great potential in the treatment of zoonotic parasitic diseases due to their antimicrobial and antiparasitic properties, as well as their ability to target specific sites precisely [25, 26]. Metallic nanoparticles, such as silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs), can have lethal effects on zoonotic pathogens, including *Leishmania* [27-29], *Toxoplasma* [30], and *Echinococcus* [31-33], by disrupting the parasites' metabolism or destroying their cell walls. Additionally, MNPs can deliver antiparasitic drugs to infected

tissues in a targeted manner, reduce side effects, and enhance the effectiveness of treatment [34, 35]. Therefore, MNPs are considered a promising tool in the fight against parasitic diseases that affect both humans and animals.

3. Toxicity and Bioaccumulation of Metal Nanoparticles

Nanotechnology holds immense potential in medicine, enabling breakthroughs like targeted drug delivery, early disease detection, and advanced tissue engineering [36, 37]. Manipulating materials at the atomic level allows for precise treatments with fewer side effects, improved imaging techniques, and even nanorobots for repairing damaged cells [38]. This revolutionary approach has the potential to transform healthcare, offering personalized and more effective solutions for complex diseases [39, 40].

Using MNPs for the treatment of zoonotic diseases is one of the most challenging tasks due to concerns about the toxicity of these particles in biological systems [41]. Previous studies have demonstrated a potential for MNPs, including AgNPs and zinc oxide nanoparticles, to induce oxidative stress, which damages DNA and disrupts cellular function as a result [42, 43]. In the majority of cases, this toxicity results from the excessive production of reactive oxygen species (ROS) within cells, which can damage the cell membrane, proteins, and genetic components of cells. Studies have shown that the toxicity of nanoparticles is strongly influenced by their size, shape, and surface coverage, i.e., smaller nanoparticles with a larger active surface area tend to cause greater toxicity than larger nanoparticles [44, 45]. Additionally, MNPs can accumulate in the tissues of vital organs, including the liver, kidney, spleen, and brain, resulting in long-term toxic effects [46].

The elimination pathways from the body that are involved in eliminating MNPs are another important factor in determining their toxicity. Evidence suggests that nanoparticles with sufficiently high concentrations can be eliminated from the body through the hepatobiliary and renal pathways after entering the bloodstream [47, 48]. Although MNPs may indeed remain in the body for an extended period, sometimes due to their binding to plasma proteins or incorporation into nanostructured structures within the body. Nanoparticles can accumulate in the body, raising concerns about their long-term effects, as nanoparticles that are not effectively eliminated may increase the risk of long-term harm [49]. Several methods can be employed to reduce the toxicity of MNPs, including designing biodegradable nanoparticles and modifying their surfaces with biocompatible polymers, such as polyethylene glycol (PEG) and chitosan, which can accelerate biodegradation and decrease accumulation in vital organs, thereby reducing toxicity [50]. Moreover, to reduce the toxicity of these nanoparticles in the treatment of zoonotic diseases, dosage adaptation and targeted drug delivery methods can be further utilized to enhance the therapeutic efficacy of these nanoparticles (Figure 1).

4. Immune and Inflammatory Responses Induced by Metal Nanoparticles

The immune system plays a crucial role in recognizing and removing foreign particles, such as MNPs, from the body. It is, however, essential to note that interactions between nanoparticles and the immune system can lead to complex consequences. MNPs, such as AuNPs and AgNPs, can induce inflammation in macrophages and dendritic cells, leading to the overproduction of inflammatory cytokines, including TNF- α , IL-6, and IL-1 β [51]. These immune responses can cause systemic inflammation and, in severe cases, lead to a condition known as cytokine storm syndrome, which poses significant risks to the patient. The effects of nanoparticles on blood proteins, including albumin and fibrinogen, may also be altered by nanoparticles, as they form protein coronas that can affect their biological function and stimulate the immune system [52].

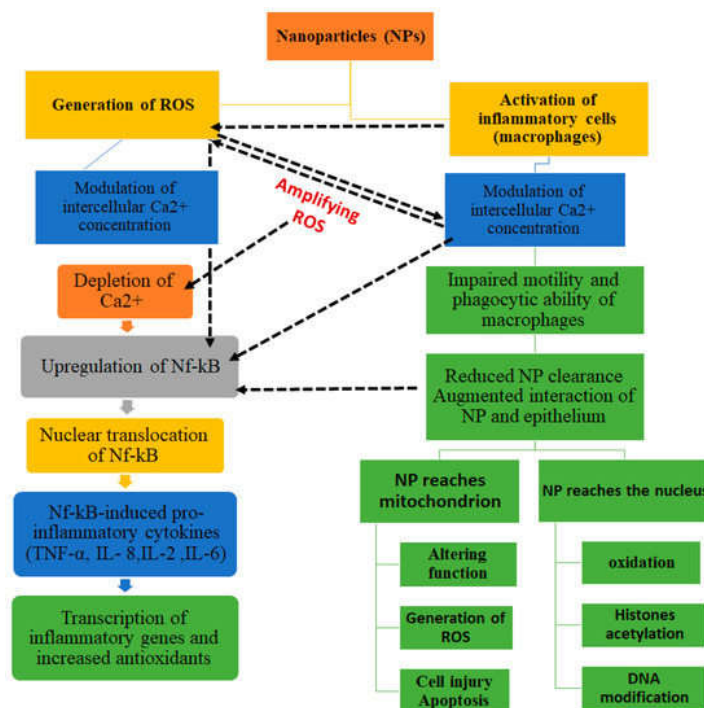


Figure 1. The most common mechanisms underlying NP cytotoxicity.

Figure 1 represents the primary mechanisms responsible for nanoparticle (NP)-induced cytotoxicity, highlighting key pathways such as oxidative stress, membrane disruption, and inflammatory responses that contribute to cellular damage [53].

However, studies have found that MNPs may cause immune system suppression in some cases, particularly when individuals are exposed to them for extended periods and at low doses [54, 55]. As a result, there is an increased risk of contracting an opportunistic infection, and the body's defense mechanisms can be compromised. To mitigate the adverse effects of nanoparticles, various strategies have been explored, including chemical modification of nanoparticle surfaces, the use of anti-inflammatory coatings, and optimal doses of nanoparticles. In this regard, biocompatible polymers, such as phospholipids, can be used as surface coatings on MNPs, reducing the interaction of immune cells with them and thus decreasing the likelihood of adverse effects, including inflammation [56]. Additionally, studies have demonstrated that hybrid nanoparticles made of noble metals and biocompatible polymers are less toxic and have fewer adverse immune effects than pure MNPs, which can be an effective alternative in treating zoonotic diseases that they may transmit (Table 1) [57].

5. Future Prospects

Several key approaches can be employed to mitigate MNP toxicity, including surface engineering and chemical modification. Studies have shown that MNPs whose surfaces are coated with biocompatible components, such as polymers, proteins, or organic compounds, are less likely to interact with healthy cells and the immune system. Consequently, their toxicity is reduced, resulting in a positive impact on the environment. Several polymer coatings, such as PEG, chitosan, and dextran, can significantly impact the half-life of MNPs in the bloodstream [9]. They can accumulate less in vital organs such as the liver and kidneys. A novel approach to producing MNPs

is the design of hybrid nanoparticles. These nanoparticles combine noble metals with biocompatible materials to create an impressive product. By using these compounds, it is possible to reduce the intrinsic toxicity of heavy metals and improve the drug delivery properties [58]. In addition, altering the crystal structure and size of MNPs is another way to mitigate the side effects of these particles, as small nanoparticles tend to exhibit higher levels of cytotoxicity. By optimizing their shape and size, it becomes easier to reduce this toxicity [59].

Table 1. Key challenges associated with MNPs in medicine and their potential solutions

Challenge	Solution
High cytotoxicity	Surface modification (PEG, chitosan)
Oxidative stress	Antioxidant coatings (vitamin E, polyphenols)
Bioaccumulation	Biodegradable nanoparticles
Inflammatory response	Anti-inflammatory surface coatings
Non-specific distribution	Targeted drug delivery (Ligands, Antibodies)
Short circulation time	PEGylation to increase stability
Uncontrolled release	Smart nanoparticles (pH-/enzyme-sensitive)
Protein corona formation	Functionalized surface modifications
Limited biocompatibility	Hybrid nanoparticles (polymer-metal)
Renal clearance issues	Optimized size & surface charge
Environmental toxicity	Green synthesis of nanoparticles
High aggregation tendency	Surfactants & stabilizing agents
Immune System activation	Use of biocompatible coatings
Poor penetration in tissue	Nano-carriers with enhanced permeability
Regulatory challenges	Standardized safety guidelines

Furthermore, developing new drug delivery technologies targeted to specific sites in the body can also play a crucial role in enhancing the effectiveness and minimizing the side effects of MNPs, particularly when combined with surface engineering. Controlled-release systems, such as nanocapsules and nanoliposomes, can regulate drug release over a specific period. They are capable of preventing the excessive accumulation of nanoparticles in sensitive tissues when used effectively. There is also a growing trend to use magnetic nanoparticles in conjunction with external magnetic fields to guide them to the specific site of infection, thereby increasing safety and reducing the unintentional dissemination of nanoparticles in the body through magnetic field-guided delivery. Furthermore, a novel approach to targeted treatment of zoonotic diseases has been investigated by examining smart nanoparticles capable of being activated in response to environmental changes such as pH, temperature, and specific enzymes. These smart nanoparticles have been shown to have critical applications for treating diseases spread by animals. It has been demonstrated that nanoparticles activated in the acidic environment inside infected tissues can exert their toxic effects only at the site of infection, thus causing no damage to healthy cells on the surrounding surfaces.

It is anticipated that future approaches will utilize artificial intelligence (AI) and bioinformatics to predict and control the toxicity of nanoparticles [60]. By analyzing the existing data gathered from toxicology studies, machine learning models can identify unknown patterns in the biological reaction of nanoparticles and provide accurate predictions about their behavior in the body as a result. In addition, molecular simulations can help elucidate the

interactions between nanoparticles and biological proteins, cell membranes, and metabolic enzymes, thereby assisting in the design of nanoparticles tailored to biological systems [61, 62]. Furthermore, the development of specialized databases, such as NanoDatabank and TOXNET, which provide comprehensive information on the toxicity of nanoparticles, can help researchers assess the safety of nanoparticles more accurately. Overall, combining advanced technologies such as bioengineering, nanotechnology, and data science can pave the way for developing safer and more efficient MNPs to treat zoonotic diseases, thereby helping to reduce the challenges in this field.

6. Conclusion

The use of MNPs in treating zoonotic diseases has been proposed as a novel and effective strategy due to their unique properties, including nanometer size, high surface-to-volume ratio, and potent antimicrobial activity. However, major challenges include cytotoxicity, bioaccumulation in vital organs, and stimulation of immune responses. Future research should focus on optimizing the design of MNPs, enhancing drug delivery technologies, and minimizing side effects to ensure MNPs can be used safely and effectively in the treatment of zoonotic diseases. Given the high potential of MNPs in the medical field, conducting more comprehensive and interdisciplinary research, as well as developing precise safety standards, can pave the way for developing new and less risky therapeutic solutions to combat zoonotic diseases.

Conflicts of Interest

The authors declare no conflict of interest associated with this manuscript.

Declaration of the Use of Generative AI

After the content was fully written, an AI-powered tool was exclusively used to review and refine the chapter's grammar, punctuation, and overall linguistic flow. The AI tool was used strictly as a proofreading and language refinement assistant and was not employed at any stage for generating content, ideas, or writing chapter sections.

Author Contributions

Athena Maleki: Methodology, Formal analysis and investigation, Writing - original draft preparation, Writing - review and editing; Davood Dorranipour: Methodology, Writing - original draft preparation, Writing - review and editing; Mohadese Sajedi-Moghaddam: Writing - original draft preparation; Mostafa Peyvandi: Methodology; Sérgio Alencar: Conceptualization, Supervision. All authors checked and approved the final version of the manuscript for publication in the present journal.,

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