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Prospective Review

The Role of Metallic Nanoparticles in the Prevention and Treatment of Parasitic Diseases in Poultry

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ABSTRACT

The development of nanotechnology for the treatment of parasitic diseases is still in its infancy. However, it is expected that this new field can provide a solution to parasitic diseases and compensate for the lack of vaccines to prevent them. It can also provide new treatment options for parasitic diseases resistant to current treatments. Nanomaterials have been developed for antibacterial and anticancer therapies. However, it is important to determine their antiparasitic potential due to the wide variety of their physicochemical properties. When designing metallic nanoparticles (MeNPs) and specialized nanosystems like MeNPs encapsulated within a drug shell, it is essential to consider several key physicochemical properties. Shape, size, surface charge, and type of surfactant control are some of these physicochemical properties. In addition to interacting with parasite cells' target molecules, shell molecules are also important. By developing antiparasitic drugs using nanotechnology and nanomaterials for diagnostics, new and effective methods of treatment and diagnostic tools for poultry diseases are expected to be available in the future to enhance poultry disease prevention and reduce morbidity and mortality rates.

1. Introduction

The choice of poultry as a protein source by millions of consumers worldwide is undeniable[1,2]. In 2019, egg production reached 83 metric tons (Mt), an increase of 63% over 2000. Approximately 40% of global meat production comes from chicken, making it the most widely produced meat[3]. There are, however, formidable challenges facing the industry, the most important of which is parasitic disease. Parasitic infections, caused by a diverse array of helminths, arthropods, and protozoa, compromise productivity, welfare, and poultry health and productivity. Some specific examples of these parasitic diseases include coccidiosis caused by the protozoan *Eimeria* species, roundworms (*Ascaridia galli*), and tapeworms (*Raillietina* species). Various parasitic infections can be treated with herbal compounds, such as avian trichomoniasis and antiprotozoal, and antimicrobial compounds, including phytogenic feed additives (probiotics), essential oils, and herbal extracts[4-6].

The effectiveness of nanoparticles (NPs) on animal feed utilization, growth performance, and health status has been demonstrated in several studies[7-9]. Micro- and macro-elements in nano-forms are the most frequent nanoparticles used to increase body weight, gain, and feed conversion ratios in the animal industry[10,11]. The NPs provide animals with the necessary elements, improve their productivity, and boost their immune profiles; immunity also decreases the risk of infection. The properties of NPs have been reported to be antiviral, antibacterial, antiprotozoal antifungal, and antioxidative. As an alternative to antibiotics, NPs of zinc (Zn), silver (Ag), gold (Au) and copper (Cu) can promote health and growth. For example, ZnONP has been found to increase Fe and Cu contents in the hepatic tissue and Zn content in the tibia, with a positive effect on mRNA expression of insulin-like growth factor-1 and growth hormone genes[12-18].

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In poultry parasitology, metal NPs can be used as innovative therapeutic agents[19]. Recent studies have investigated green synthesis methods for producing metal NPs[20,21]. Positive results have been achieved against pathogens, fungi, helminths, and cancer cells. Several compounds are being researched which are profitable, such as AgNPs[22]. As a result of studying AuNPs in colloidal systems, Michael Faraday first reported on their optical properties in 1857[23,24]. There are several uses for nano-sized structures in treating, controlling, diagnosing, and monitoring infectious diseases[25]. The chemical, mechanical, and optical properties of these NPs are well-defined[26]. The cytotoxic properties of these NPs, which depend on their form, size, charge, stability, and purity, have been demonstrated to be highly effective in treating parasitic infections[27,28].

The current study aimed to review the mechanisms underlying the interactions between metal NPs and poultry parasites. The specific types of metal NPs that have demonstrated noteworthy antiparasitic properties, such as Cu, Au, Ag, and Zn-NPs, were reviewed. This review discussed the future of treating poultry parasitic diseases with metal NPs and its challenges. Notably, nanodrugs can become a fundamental part of modern medicine in the coming years. Potential metals showed promising results when used to treat parasitic diseases as metal NPs have indicated synergistic activity with commercial antibiotics.

2. Methodology

The search engines used for retrieving published data (from 1987 to 2023) included universally recognized databases, including PubMed, Web of Science, Scopus, springer Link, Science Direct, and Google Scholar. The searching process was accomplished using some terms alone or in combination, such as (“poultry” OR “Parasite disease” OR “Metallic Nanoparticles” OR “Nanotechnology”) AND (“parasite” OR “Antimicrobial activity”), leading to 620 studies. After removing duplicates and excluding ineligible reports, 195 articles were eligible to be included in this review. Finally, 80 relevant articles with complete abstracts were included in the study.

3. Mechanisms of action of metal nanoparticles

An important characteristic of metal NPs is their ability to interact with parasites on many levels, triggering cascades of events that can result in parasite inhibition or destruction[29]. The primary mechanism of metal nanoparticle adhesion to parasites is electrostatic interaction[30]. Surface functional groups on NPs and parasite structures may facilitate the initial binding. The binding process is initiated when negatively charged NPs, such as AgNPs, interact with positively charged parasite surfaces[31].

By binding to the parasite’s outer layer, metal NPs can penetrate its interior compartments[32]. This penetration can be facilitated depending on the size and surface properties of the nanoparticle. A number of reports have shown that nanoparticle size is a significant factor in the interaction between NPs and biological systems[33,34]. Furthermore, particle size affects solubility as well as surface-to-mass ratios[35]. Due to their smaller surface area, small NPs are more receptive to functional molecules since they have more attachment sites. Upon entering the cell, metal NPs can disrupt vital cellular processes[36]. AgNPs disrupt metabolic pathways, mitochondrial function, and membrane integrity in parasites[37]. Disruptions can impair parasite survival and replication by compromising their structural integrity and functionality.

Nanoparticles’ shape also influences their interaction with parasites[38]. Anisotropic shapes like nanorods or nanowires have distinct advantages in surface area, and interaction points[39]. These geometries can enhance NP-parasite interactions and binding and disruption by offering multiple contact points. Further, NP surface properties, including functional groups and charge, can affect cellular uptake and binding strength[40].

Besides interacting with parasites directly, metal NPs affect the host’s immune response, causing a complex interplay that affects disease progression[41]. Nanoparticles enhance antigen presentation and phagocytosis by stimulating immune system cells, such as macrophages and dendritic cells[42]. As a result of these immune activations, parasites can be cleared, and a protective immune memory can be established[43].

Additionally, metal NPs modulate cytokines by modulating cytokines to balance pro-inflammatory and anti-inflammatory responses. This modulation can be leveraged to fine-tune the immune environment, potentially suppressing excessive inflammation while promoting an effective immune defense against parasites[44].

4. Types of metal nanoparticles used against poultry parasites

4.1. Silver nanoparticles

The remarkable antimicrobial activity of AgNPs has attracted significant attention regarding parasites and bacteria[45]. Several mechanisms are involved in the action of AgNPs, including disruption of cell membranes, apoptosis-induced, and parasite destruction induced by reactive oxygen species (ROS)[46]. The ROS is the most likely signaling pathway for intracellular stress responses[47]. *Eimeria* spp., could be susceptible to AgNPs in poultry parasites and needs to be investigated. Biosynthesized AgNPs were tested *in vitro* and *in vivo* against *Cryptosporidium parvum* (*C. parvum*) oocysts for antiprotozoal activity. *Cryptosporidium parvum* oocyst viability was significantly inhibited by biosynthesized AgNPs in an in vitro experiment[48].

4.2. Copper nanoparticles

Copper nanoparticles have been shown to hinder parasite growth and viability[49]. The CuNPs produce ROS when they contact parasite biomolecules, including proteins, lipids, and nucleic that play essential roles in living organisms. These molecules are the building cell layers of life and are involved in various biological processes that are crucial for the functioning and survival of organisms[50]. Furthermore, oxidative stress disrupts critical cellular functions and can affect cell growth[51]. CuNPs are effective against poultry parasites such as *Ascaridia galli*. Their effects inhibit the parasite's ability to move and absorb nutrients by interfering with its cuticle and internal tissues[52]. *Eimeria tenella* is one of the most pathogenic coccidias. Copper and Zn demonstrated significant antimicrobial and antiparasitic activity against coccidia[53].

4.3. Zinc nanoparticles

As a result of their multifaceted modes of action, ZnNPs have emerged as potential inhibitors of poultry parasites[54]. By disrupting membrane integrity and causing oxidative stress, ZnNPs hinder parasite survival. In addition to their antifungal, antimicrobial, anti-diabetic, and antiparasitic properties, Zinc Oxide Nanoparticles (ZnONPs) are used as growth promoters, immune modulators, dietary supplements, and catalysts for phytochemical reactions[55]. Moreover, ZnONPs can be used in targeted drug delivery, biological labeling, biological sensing, and gene transport. There have been positive results reported in prior studies regarding broiler productivity, gastrointestinal function, and antioxidant status[56]. *Trichomonas gallinae* (*T. gallinae*) is one of the most serious bird diseases[57]. Poly(rhodanine)-coated zinc oxide NPs were tested against *T. gallinae* parasite *in vitro,* and positive results were found[58]. Coccidial disease is one of the most serious parasitic diseases affecting poultry farms[59]. Despite various measures (such as good management, improved breeding methods, and sterilization to prevent chicks from eating mature oocysts) developed to limit its spread, this protozoan causes significant economic losses. As a result, ZnONPs were examined for their antiparasitic activity against *E.tenella*-infected broilers[60].

4.4. Gold nanoparticles

Through their antiparasitic and immunomodulating properties, AuNPs are unique in managing poultry parasites[61]. The AuNPs disrupt parasites' cellular membranes, interfere with intracellular signaling, and trigger apoptosis-like processes. A further benefit of AuNPs is that they can modulate a host's immune response[62]. Their effects can stimulate immune cells and enhance the production of cytokines, creating an environment conducive to parasite elimination. As a result of their immunomodulatory properties, AuNPs can improve the host's ability to recognize and combat parasites[63]. While research on AuNPs against poultry parasites is evolving, their potential to bolster the host's immune defenses offers a novel avenue for parasite control[64]. The AuNPs are used as adjuvants for immunization against bacterial and viral diseases and as vaccines against parasites[65]. Vaccines and antibodies against more than 45 viral, bacterial, and parasitic pathogens have been prepared with AuNPs. In this case, AuNPs have ranged in size from 2 to 100nm[66].

5. Combining nanoparticles with other therapies to prevent resistance

It has been well documented that the emergence of drug resistance is a recurrent challenge in managing diseases, including using metal NPs[67]. There is a possibility that parasites could evolve mechanisms to counteract the effects of metal NPs, thus reducing their efficacy over time. Parasites can use several adaptive mechanisms to evade metal NPs, such as modifying the composition of the parasite membranes to prevent nanoparticle binding, enhancing detoxification processes, or enhancing antioxidant defenses to counter nanoparticle-induced oxidative stress[68]. In order to develop effective strategies for preventing or mitigating the development of resistance, it is crucial to understand these resistance mechanisms at the genetic and molecular levels[69].

The combination of metal NPs with traditional chemical drugs therapeutic agents is one promising approach to circumvent resistance[70]. This strategy leverages synergistic effects to enhance treatment outcomes by leveraging the synergistic effects of the combined agents. When multiple mechanisms are used simultaneously to eradicate parasites, the likelihood of resistance erupting is diminished[71]. Using metal NPs in combination with conventional antiparasitic drugs or natural compounds can potentiate the overall antiparasitic effect. With the NPs, parasite membranes or vital processes are disrupted, whereas the added agents can be directed at distinct pathways so that resistance can be developed through an impenetrable barrier.

6. Rotating nanoparticle treatments

Rotational therapy is an antimicrobial resistance management strategy that can also be applied to metal NPs[72]. Changing the types of NPs or combining different types of NPs periodically enables the selective pressure on parasites to be diversified and thus more effective. As a result of this approach, parasites are less likely to adapt to a specific nanoparticle treatment regimen and develop resistance to it. Rotation prevents the parasites from being exposed to a single type of nanoparticle for an extended period of time, which makes it difficult for them to mount effective resistance mechanisms[73].

Moreover, the rotational treatment approach can extend beyond NPs to encompass a wide variety of antiparasitic agents, resulting in a dynamic treatment landscape that reduces the likelihood of resistance selection[74].

7. Challenges and advancements in nanoparticle delivery

There are several challenges that must be overcome for metal NPs to be successfully delivered to parasites[75]. For NPs to reach their intended sites of action, they must navigate biological barriers such as cellular membranes and mucosal surfaces[76]. Nanoparticles' size, charge, and surface modification have a significant influence on their interactions with biological barriers[77]. As nanoparticle engineering has progressed, surface modifications have been created that enhance the cellular uptake of NPs, facilitate transport across barriers, and increase the stability of NPs within biological fluids under varying conditions[78].

Multifunctional NPs with therapeutic and imaging properties have been developed in recent years using nanotechnology. Distribution and activity within the host, providing valuable insights regarding their pharmacokinetics and pharmacodynamics. The development of surface functionalization of NPs has also enabled the active targeting of specific parasite cells or tissues, thereby maximizing the accumulation of NPs at the site of infection.

In addition to consideration of the potential immunogenicity, cytotoxicity, and long-term effects on poultry health of nanoparticle delivery systems, it is essential to acknowledge that these systems need to be thoroughly evaluated[79].

8. Future prospective

The diverse mechanisms of action of NPs have led to the identification of these particles as promising candidates to combat poultry parasitic diseases.

However, despite the potential of NPs, there are a number of challenges that need to be addressed, such as the stability of the particles, their potential environmental impact, and optimal dosing strategies to make them effective and safe for use in poultry farms.

There has been some evidence that copper NPs can impede the viability and growth of parasites. As a result of their interaction with parasite species, CuNPs produce ROS, which damages the genetic material of the parasite and interferes with critical cellular functions. A number of challenges need to be overcome, such as understanding the correct concentration of drug to avoid toxicity while maintaining efficacy and taking into account potential adverse effects on the environment.

The ZnNPs have emerged as one of the most effective and versatile inhibitors of poultry parasites. Several challenges must be overcome while using these products to improve broiler productivity and gastrointestinal function, including optimizing dosages, understanding potential accumulation, and ensuring minimal adverse effects on beneficial microorganisms.

By combining antiparasitic properties with immunomodulation properties, AuNPs provide a unique approach to managing poultry parasites. In addition to the potential for AuNPs to strengthen immune defenses against parasites, research is underway in order to learn more about their application in bolstering immune defenses against parasites.

Considering the future of poultry parasite management, it is essential to continue researching the application of NPs in the management of poultry parasites. Several challenges have to be addressed in order to ensure the safety of NPs as well as address the potential environmental impacts of their use. With the development of nanoparticle research, there may be novel avenues for more effective and sustainable parasite control in poultry farms that can improve bird health and reduce financial losses. There is no doubt that NPs can effectively combat poultry parasites, but there are a few challenges to overcome. Developing effective delivery systems and ensuring that NPs are produced consistently and safely are crucial steps in the development process. Researchers, veterinarians, and industry stakeholders must collaborate to put NP research findings into practical solutions for sustainable poultry production.

The advancement of nanoparticle research could lead to developing strategies for managing parasites tailored to each individual. It could benefit the treatment efficacy and minimize unintended consequences if NP treatments could be customized according to parasite type and host characteristics to maximize treatment effectiveness. A combination of multiple nanoparticle types with complementary mechanisms of action could result in a synergistic effect, leading to more potent and multifaceted parasite control. By targeting parasites through multiple pathways, it is thought that these NP cocktails could revolutionize disease management. As a result of the advancements in nanotechnology, it is possible to develop innovative sensors that can detect the presence of parasites, assess their susceptibility to NPs, and monitor their populations continuously. The use of NPs in vaccine formulations could enhance the host's immune response, thereby improving the efficacy of vaccines against poultry parasites. Nanoparticles could be used as adjuvants, fostering a robust immune response and resulting in long-lasting protection.

Using NPs, future research might examine ways to enhance the genetic resistance of poultry breeds against specific parasites. This can be accomplished using NPs that stimulate specific immune responses or modify genes associated with parasite resistance. The concept of precision_agriculture could extend to nanoparticle-based treatments. To maximize the efficacy of NPs, their use could be optimized by delivering them precisely where they are needed, reducing the tendency for wastage and environmental harm.

Scientists could concentrate their efforts on designing biodegradable NPs or formulations of NPs that, after being used for their intended purpose, degrade naturally over time. As a result, concerns about the long-term impact on the environment would be alleviated.

By combining nanoparticle-related data with advanced analytics, it may be possible to create predictive models for disease outbreaks and treatment responses based on nanoparticle data. As a result, international collaboration between researchers, industry stakeholders, and policymakers is needed to overcome challenges associated with nanoparticle use in poultry production. It is possible to overcome obstacles and ensure responsible nanoparticle application by sharing knowledge and best practices.

9. Conclusion

The use of metal NPs could bring about a novel approach to controlling poultry parasitic diseases due to their diverse mechanisms of action. Several NPs, such as copper, silver, gold, and zinc NPs, have been demonstrated to disrupt parasites, induce oxidative stress in cells, and modulate immune responses. Nevertheless, further research is needed to develop a complete understanding of the interactions and resistance mechanisms and ensure safety in the future. In order to translate nanoparticle-based interventions to commercial farms while addressing safety concerns and ensuring that regulatory requirements are met, researchers, veterinarians, producers, and regulators must work collaboratively together. As a key component of the poultry industry's parasite management system, metal NPs offer a revolutionary approach. Nanoparticle development and deployment should be accompanied by comprehensive toxicological assessments to ensure the safety of poultry and poultry product consumers.

Declarations

Competing interest

The authors declare no conflict of interest.

Authors' contribution

Nima Komeili played a pivotal role in the conceptualization phase of this project. When it came to methodology, the collective efforts of all authors contributed significantly to the development of the research approach. The formal analysis and investigation stages benefited from the collective contributions of all authors, showcasing their dedication and expertise. In terms of the initial draft preparation and subsequent revisions, the entire authorship team worked collaboratively to ensure the quality and coherence of the content. Lastly, Nima Komeili provided valuable supervision throughout the project, guiding and overseeing the research activities. In summary, this research project was a collaborative endeavor with Nima Komeili taking on a supervisory role, while all authors actively participated in various aspects, from conceptualization to writing and analysis. All authors checked and approved the final version of the manuscript for publication in the present journal.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical considerations

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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