Using of Nanoparticles in treating of Hydatid Disease in Domestic Animals

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Abstract:
The parasite *Echinococcus granulosus* is the cause of unilocular hydatid disease, which is a serious health risk to people and domestic animals worldwide. Livestock with hydatid disease suffers substantial financial losses due to the slaughterhouse's disapproval of the diseased animal parts, productivity losses (such as lowered live weight gain, milk yield, reproductive rates, and hide and skin value), and expenses related to caring for both humans and animals. Because of the parasite's complex life cycle and the difficulties associated with traditional treatment techniques, new strategies are needed to handle this crippling illness more successfully. In the treatment of hydatid illness, nanomedicine and nanoparticles have shown great promise, providing new approaches to medication distribution, focused therapy, diagnosis, and control measures. The possible roles and applications of nanomedicine and nanoparticles in treating hydatid illness in domestic animals are reviewed in this article. Owing to their distinct physicochemical characteristics at the nanoscale, nanoparticles enable tailored medication administration, enhancing anthelmintic agent potency while reducing systemic side effects. Therapeutic drugs like praziquantel or albendazole can be encapsulated in these nanoparticles, allowing for improved permeability and retention at the location of the parasite cysts. Additionally, imaging agents and diagnostic instruments at the nanoscale enable.

Additionally, nanotechnology offers avenues for developing innovative control measures, including environmental disinfection and targeted delivery of parasiticides. Collaborative efforts between researchers, veterinarians, and experts in nanotechnology are crucial to harnessing the full potential of nanoparticles and nanomedicine in effectively managing the infection in domestic animals.

Keywords: Hydatid Disease, Cystic Echinococcosis, Zoonosis, Nanoparticles, Nanomedicine, Treatment.

Introduction

Hydatid disease, is one of the most vital zoonotic parasitic diseases throughout the world, carrying a significant risk to public health as well as significant financial damages (Romig et al., 2011). It is caused by the larval morphological stage (hydatid cyst) of *Echinococcus* and represents a serious risk to one's health to both
humans and animals globally (Rokni, 2009; Chalechale et al., 2016).

Its intricate life cycle and the complex nature of the cysts it forms within vital organs present formidable challenges in its treatment (Rokni, 2009). However, the emerging field of nanomedicine offers promising avenues for addressing this ailment. Utilizing nanoparticles (NPs) in combating disease in ruminants and humans represents a groundbreaking approach with immense potential for targeted therapy and improved treatment outcomes (Sadr et al., 2023).

NPs, due to their unique physical and chemical properties at the nanoscale, have garnered attention as innovative tools in medical interventions (Altammar, 2023). These tiny structures hold immense promise in various aspects of treatment. Their size is small allows for enhanced permeability and retention at the site of the cysts, enabling precise delivery of therapeutic agents (Soltani et al., 2017). Moreover, NPs can encapsulate, protect, and deliver drugs or therapeutic molecules to specific locations within the body, mitigating off-target effects and improving drug efficacy (Yusuf et al., 2023).

The multifunctional nature of NPs allows for diverse applications in hydatid disease management (Jamshidi et al., 2008). They can be engineered to carry antiparasitic agents, such as praziquantel or albendazole, directly to the cysts, thereby increasing drug concentrations at the target site while minimizing systemic exposure (Jamshidi et al., 2008; Yusuf et al., 2023). Furthermore, NPs can serve as diagnostic tools, facilitating early detection and monitoring of disease progression through imaging modalities or biomarker detection, enabling timely intervention (Thwala et al., 2023).

In domestic animals, where the disease poses a significant economic burden and a zoonotic risk, nanoparticle-based interventions offer an opportunity for more effective and targeted treatment (Bai et al., 2018). By enhancing drug delivery and reducing the required dosage, NPs could potentially alleviate the development of drug resistance commonly observed in conventional therapies (Lee et al., 2019).

However, while the potential of nanomedicine in combating hydatid disease is promising, challenges such as the safety profile, biocompatibility, and scalability of nanoparticle-based therapies remain. Research efforts are ongoing to address these concerns and optimize the use of NPs for safe and efficient hydatid disease management (Zhang et al., 2023). The goal of this article review is to review the possible applications and effects of nanomedicine and nanoparticles in treating hydatid illness in domestic animals.

Classification and Life Cycle

*Echinococcus granulosus* (*E. granulosus*) is a parasitic tapeworm responsible for causing echinococcosis (hydatid disease) (Assefa et al., 2015; Chalechale et al., 2016). *E. granulosus* is as follows: *E. granulosus* is under Kingdom: Animalia, Phylum: Platyhelminthes, Class: Cestoda, Order: Cyclophyllidea, and Family: Taeniidae (Romig et al., 2015).

*E. granulosus* has a complex life cycle involving definitive hosts (usually canids such as dogs, wolves, and foxes) and intermediate hosts (often herbivores like sheep, goats, cattle, and occasionally humans) as mentioned in Fig.1 (Mandal, 2006; Govindasamy et al., 2023). The life cycle of *E. granulosus* demonstrates its adaptation to a definitive host, where it reproduces sexually, and an intermediate host, where it forms cysts, ensuring the transmission and continuation of the parasite between these hosts (Govindasamy et al., 2023).

Alternatively, intermediate hosts can act as accidental intermediate hosts by ingesting eggs directly from contaminated sources. Once ingested, the oncospheres are released from the eggs in the intestine of the intermediate host. These oncospheres penetrate the intestinal wall and migrate through the circulatory system to various organs, predominantly the liver and lungs, where they develop into fluid-filled cysts called hydatid cysts (Pednekar et al., 2009). Within the intermediate host, these cysts grow slowly and produce protoscolices and daughter cysts inside them. An intermediate host is
consumed by a dog (final host), and the protoscolices present in the hydatid cysts can develop into adult tapeworms in the small intestine of a dog, completing the life cycle (Mandal, 2006).

*E. granulosus* has several distinct features in its life cycle, involving different stages and intermediate hosts where the larvae develop into hydatid cysts primarily in the liver and lungs of intermediate hosts. These cysts contain fluid-filled bladders containing numerous protoscoleces, which are potential infective agents for the definitive host upon ingestion (Romig et al., 2017).

Understanding the life cycle and classification of *E. granulosus* is crucial in developing strategies for the prevention, control, and treatment of hydatid disease, which remains a significant public health concern in many regions worldwide (Eckert & Deplazes, 2004).

Structure of Hydatid Cyst

The hydatid cyst, formed within the intermediate, consists of several layers that encase the developing larvae and protoscolices (Golzari & Sokouti, 2014). The composition and structure of cyst is typically organized into the following layers:

1. Outer Layer (pericyst): This outer layer is a protective covering formed by the host’s tissue reaction to the parasitic infection. It is primarily composed of fibrous connective tissue derived

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**Figure 1. Life Cycle of Hydatid Disease**

*Source: Govindasamy et al., 2023*
from the host, encapsulating the cyst and confining its contents, as shown in Figure 2 (Pedrosa et al., 2000).

2. Laminated Layer: The laminated layer is the innermost layer of the hydatid cyst and is characteristic of *E. granulosus*. It consists of multiple acellular layers arranged in a laminar fashion, resembling an onion-like structure. This layer is secreted by the germinal layer, as shown in Fig. 2 (Golzari & Sokouti, 2014; Sokouti et al., 2014).

3. Germinal Layer: This is the innermost cellular layer of the cyst, found beneath the laminated layer. It is actively involved in producing brood capsules and protoscolices, which are the infective forms of the parasite. The germinal layer continually generates the daughter cysts and protoscolices, contributing to the growth and expansion of the cyst, as shown in Figure 2 (Thompson & McManus, 2000; Sokouti et al., 2014).

4. Hydatid Fluid: This is a clear, colorless, or slightly yellowish fluid known as hydatid fluid. This fluid fills the cyst's internal cavity, providing an environment necessary for the growth and development of the larvae and protoscolices (Thompson & McManus, 2000). The fluid also contains nutrients and immunomodulatory factors required for the parasite's survival.

The hydatid cyst structure serves as a protective environment for the developing larval stage of *E. granulosus*. These cysts can grow slowly over time and can reach considerable sizes, causing pressure on surrounding tissues and potentially leading to complications if left untreated (Fan et al., 2020). Surgical intervention or pharmacological treatments are often required to manage hydatid cysts and prevent their rupture, which can lead to severe health issues or the dissemination of the parasite within the body (Derici et al., 2006).

**Treatment of Hydatid Disease in Ruminants**

The treatment of hydatid disease in ruminants (such as sheep, goats, and cattle) typically involves a combination of measures aimed at reducing the prevalence of the disease and preventing its transmission (Banda et al., 2012). However, it's important to note that there is no single treatment that can eliminate the infection in these animals (Tamarozzi et al., 2014). There are five options currently available for the treatment of cystic disease:

1. **Treatment by using Anthelminthic**

   In some cases, anthelminthic drugs such as praziquantel or albendazole may be administered to infected animals. These drugs can help reduce the viability of the cysts and potentially prevent the development of new cysts. However, their effectiveness can vary, and complete elimination of the infection may not be achieved through drug treatment alone (Velasco-Tirado et al., 2018).

2. **Surgical Intervention**

   Surgical removal of cysts might be considered in certain situations where cysts are large, accessible, and causing significant health issues in the animal. Surgical procedures can involve cystectomy or pericystectomy, aiming to remove the cysts and surrounding tissues to minimize the risk of recurrence (Birnbaum et al., 2012; Sozuer et al., 2014).

3. **Hygiene and Management Practices**

   Implementing good hygiene practices is crucial in preventing the spread of the disease within
herds. Proper disposal of infected organs, avoiding contamination of grazing areas with feces containing Echinococcus eggs, and preventing access of definitive hosts (such as dogs) to livestock can help reduce the risk of transmission (Craig et al., 2007).

4. Quarantine and Control Measures
Quarantine measures may be implemented to prevent the movement of infected animals to new areas or herds. Additionally, control measures, including regular deworming of dogs and surveillance programs, can contribute to reducing the prevalence of the disease in livestock (Eisenman et al., 2023).

It's important to note that preventing hydatid disease in livestock involves a multifaceted approach, including both treatment strategies for infected animals and preventive measures to limit the spread of the disease within and between animal populations. Collaboration between veterinarians, livestock owners, and public health authorities is crucial in implementing effective control and prevention measures to minimize the impact of hydatid disease in ruminants (Craig et al., 2007; Eisenman et al., 2023).

Nanomedicine
Nanomedicine offers several potential applications in the treatment of hydatid disease in ruminants, aiming to improve therapeutic outcomes and control the spread of E. granulosus infections in livestock (Norouzi et al., 2020; Sadr et al., 2023). Here are the potential roles and applications of nanomedicine in addressing hydatid disease in ruminants:

1. Nanoparticles can be utilized to enhance the delivery of anthelmintic drugs used to treat E. granulosus infections in ruminants. Nano-based drug delivery systems can improve drug stability, bioavailability, and targeted delivery to the site of the infection, potentially increasing the effectiveness of treatment (Sadr et al., 2023).

2. Encapsulation of anthelmintic agents within nanoparticles can protect these drugs from degradation in the gastrointestinal tract, ensuring a more sustained and controlled release of the therapeutic agent at the target site, such as Echinococcus cysts in the liver or lungs of infected animals (Norouzi et al., 2020; Hamid et al., 2023).

3. Functionalized nanoparticles can be designed to specifically target Echinococcus cysts in ruminants (Deng et al., 2021). These nanoparticles can be engineered to recognize and bind to specific molecules or structures present on the surface of the cysts, facilitating the localized delivery of therapeutic agents to the site of the infection while minimizing systemic exposure (Albalawi et al., 2020).

4. Nanotechnology-based drug delivery systems may help mitigate the development of drug resistance commonly observed with conventional anthelmintic treatments. By enhancing drug efficacy and minimizing the required dosage, NPs could potentially reduce the emergence of resistance in Echinococcus parasites (Soltani et al., 2017; Sadr et al., 2023).

5. NP-based vaccine delivery systems can aid in the development of more effective vaccines against E. granulosus in ruminants. These systems can improve the immunogenicity and delivery of vaccine antigens, potentially leading to enhanced protective immune responses in infected animals (Bezbaruah et al., 2022).

6. NPs can contribute to the development of sensitive and specific diagnostic tools for detecting Echinococcus infection in ruminants. Nanoscale diagnostic devices, including biosensors and imaging contrast agents, could enable early and accurate detection of the parasite, facilitating timely intervention (Jahani et al., 2014).

Effects of Nanomedicine on Protoscolices
The protoscolices are the infective stage of E. granulosus found within the hydatid cysts. The ability of nanoparticles to act as protoscolicidal agents against E. granulosus protoscolices has been explored in scientific research.
NPs have shown potential as protoscolicidal agents due to their ability to penetrate tissues and exhibit specific interactions at the nanoscale level (Norouzi et al., 2020). Some studies have investigated the protoscolicidal activity of various types of nanoparticles, including copper nanoparticles, silver nanoparticles, zinc oxide nanoparticles, and others, against protoscolices (Shnawa, 2018).

Research has Indicated that Certain NPs Possess Protoscolicidal Effects

1. Silver NPs have been reported to exhibit protoscolicidal activity against *E. granulosus* protoscolices. Their antimicrobial properties have been studied in vitro and in animal models, showing efficacy in killing protoscolices (Salih et al., 2020).

2. Zinc oxide NPs and copper nanoparticles have also been investigated for their protoscolicidal effects. Studies have shown their potential to induce damage and kill *E. granulosus* protoscolices in vitro (Shakibaie et al., 2022).

3. Polymeric nanoparticles loaded with specific drugs or substances with known scolicidal properties have been researched for their effectiveness in killing protoscolices. These NPs can provide sustained release and targeted delivery of scolicidal agents to the site of infection (Çolak et al., 2019).

The protoscolicidal activity of NPs often involves disrupting the integrity of the protoscolex, causing structural damage, membrane disruption, or interfering with vital metabolic processes, ultimately leading to the death of the parasite (Raziani et al., 2023).

However, despite promising results in laboratory studies, there’s still a need for further research to determine the efficacy, safety, and optimal conditions for using nanoparticles as protoscolicidal agents. Additionally, the translation of these findings into practical clinical applications for treating hydatid disease in animals requires thorough investigations into their biocompatibility, dosage, mode of administration, and potential side effects to ensure their effectiveness and safety in vivo.

Discussion

Numerous issues have made standard chemotherapy less effective for treating hydatid cysts (Manterola et al., 2023). One of the biggest obstacles is that cysts typically form in intricate anatomical locations that are challenging to access within the body. When chemotherapeutic drugs are given systemically, insufficient drug concentrations are consequently present on cyst surfaces, which frequently results in unsatisfactory treatment outcomes (Aminu et al., 2020).

The hydatid cyst is protected by a thick, layered membrane that envelops it (Majumder et al., 2019). Drug exposure is decreased by this barrier, which prevents therapeutic drugs from accessing the contents of the cyst. The therapeutic effects are thereby lessened. Nanotechnology offers a novel means of getting around these challenges and offers a chance to enhance drug delivery methods (Geramizadeh, 2017). Chemotherapeutic chemicals can be more soluble, stable, and accessible when encapsulated in nanocarriers, which enables more accurate and effective drug delivery to cysts (Momčilović et al., 2019).

The rapid detection and precise diagnosis of hydatid cysts are critical to the efficacy of treatment. The most widely utilized diagnostic methods at the moment are computed tomography and ultrasound, with serology testing serving as a complement (AlGabbani, 2023). However, there are numerous shortcomings with these well-established methods (Aljanabi et al., 2021). When imaging does not provide a clear and complete view, there is a chance of insufficient characterization of cysts or false negative results. However, serological testing lacks the sensitivity and precision required for early detection (Deng et al., 2019).

Targeted medicine distribution to cyst sites is one of the most important features of nanoparticles. In particular, nanocarriers are capable of effectively delivering medications across cysts via intricate circulatory paths (Xu et al., 2022). While it is evident that nanotechnology has potential for hydatid cyst treatment, there are several drawbacks as well. The primary source of health
issues with nanomaterials is their poisonous nature (Olawoyin, 2018). Extended-term effects of nanoparticles require extensive safety analyses and biocompatibility studies. The safety and well-being of the host must always come first, from the start of the formulation process until the end of the nanotherapeutics application phase (Abdussalam-Mohammed, 2019).

Conclusion

The emerging of nanomedicine and the application of NPs offer promising avenues for addressing the challenges posed by hydatid disease in domestic animal health. The intricacies of the parasite’s life cycle, coupled with limitations in traditional treatment methods, necessitate innovative approaches for effective management of this debilitating condition.

NPs are characterized by their unique physicochemical properties at the nanoscale, present opportunities for targeted therapy, improved drug delivery, advanced diagnostics, and innovative control measures in combating hydatid disease. Encapsulating anthelmintic agents within NPs facilitates targeted drug delivery to the parasitic cysts, potentially enhancing treatment efficacy while minimizing systemic side effects.

However, while the potential of NPs and nanomedicine in treating hydatid disease in domestic animals is promising, there remain challenges in ensuring the safety, biocompatibility, and scalability of these innovative approaches. Further research and collaborative efforts among researchers, veterinarians, and nanotechnology experts are essential to overcome these challenges and translate these advancements into practical clinical applications.

Future Directions

In the future, treating hydatid disease with nanotechnology will open up several research and development opportunities. The field can go further with the creation of numerous unique treatment options. The development of NPs according to particular specifications will determine future advancements.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the research data and tools used in this study.

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Author Contributions

All authors conceived this work and drafted and finalized this review article.

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