Iranian Journal of Basic Medical Sciences
ijbms.mums.ac.ir

Recent advances in the detection and treatment of hydatid cysts by nanomaterial-based carriers

Nozhat Zebardast [1]*, Farid Ajori [2, 3], Rahim Nosrati [1, 2]*

[1] Cellular and Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[2] Student Research Committee, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[3] Department of Parasitology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

ARTICLE INFO

Article type:
Review

Article history:
Received: Sep 5, 2025
Accepted: Feb 22, 2026

Keywords:
Albendazole (ABZ)
Cystic Echinococcosis
Drug delivery
Hydatid cyst
Nanocarriers
Nanoparticle

ABSTRACT

Cystic echinococcosis (CE) is a neglected parasitic disease. Although several therapeutic approaches are available for CE, including PAIR (Puncture, Aspiration, Injection, Re-aspiration), surgery, chemotherapy with anthelmintic drugs, and waiting for inactive cysts, these methods face challenges, and treatment choices remain debated. Regarding chemotherapy, especially with albendazole (ABZ) as the first-line drug, efficacy is limited by poor solubility and low bioavailability. Recently, nanoparticle (NP)-based systems, or nanocarriers, have attracted much interest in drug delivery, with ABZ as the main focus. This review summarizes the latest progress in developing diverse nanocarrier systems, such as liposomes, polymeric NPs (PNPs), and metallic NPs, highlighting their potential for scolicidal activity and for improving therapeutic approaches for CE. In addition, diagnostic methods, including imaging techniques and serological tests, as well as emerging nanotechnology-based approaches such as biosensors and nanosensors are briefly discussed to provide a more comprehensive perspective on CE management. Subsequently, the prospects and challenges of drug-loaded nanocarriers for the treatment of CE are briefly discussed to further encourage their use as a means to improve drug delivery performance in CE therapy.

▶Please cite this article as:
Zebardast N, Ajori F, Nosrati R. Recent advances in the detection and treatment of hydatid cysts by nanomaterial-based carriers. Iran J Basic Med Sci 2026; 29:

Introduction

Hydatidosis and cystic echinococcosis

Hydatidosis is a neglected cyclozoonosis disease resulting from the larval stage (metacestode or hydatid cyst) of *Echinococcus* species cestodes. The most common species of the *Echinococcus* genus are *Echinococcus granulosus* and *Echinococcus multilocularis*, which are primarily responsible for cystic echinococcosis (CE) and alveolar echinococcosis (AE), respectively (1, 2). Humans are considered accidental hosts of hydatidosis, which can be contracted by eating contaminated water or food with parasite eggs or through contact with an infected animal. The parasite often emerges into a fluid-filled hydatid cyst in the lungs and liver (2). In the liver, the cyst of *E. granulosus* at the maturing stage is composed of three distinct layers: the outer pericyst, the parasite-derived laminated layer, and the inner germinal layer (3)(Figure 1).

Hydatidosis is a globally distributed zoonotic disease with a prevalence reaching up to 5% to 10% in endemic areas (4). Hydatidosis is endemic in regions such as the Mediterranean basin, parts of South America, North and East Africa, the Middle East, China, and the Indian subcontinent, where livestock rearing is common. On the contrary, New Zealand, Malta, and Australia have largely controlled the disease through effective public health interventions (5, 6). Both CE and AE represent a significant disease burden, which might be fatal in infected people with severe clinical syndromes (7). In patients with CE, the mortality rate after surgery has

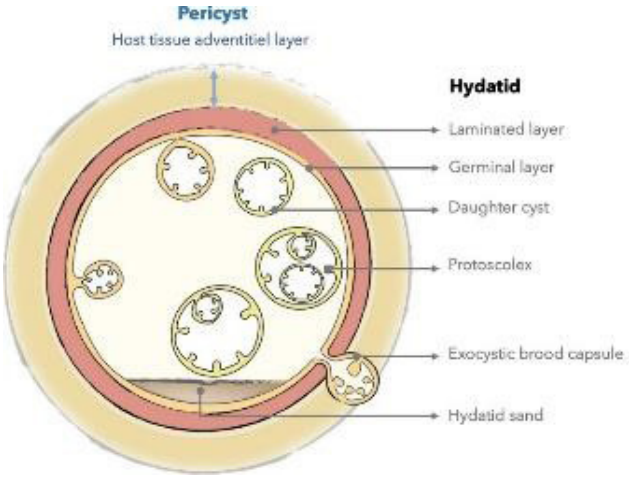

Figure 1. Schematic structure of a cystic echinococcosis cyst
Reprinted with permission from Calame *et al.*, published under a CC BY 4.0 license

***Corresponding authors:** Nozhat Zebardast. Cellular and Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran, Email: nszebardast@gmail.com; Rahim Nosrati. Cellular and Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran, Student Research Committee, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran. Email: Rahim_nosrati@gums.ac.ir

been estimated to be 2.2% on average, and the recurrence rate after medical intervention is 5.6% (7). Beyond the costs associated with medical treatment, a significant financial loss has been reported in the livestock industry due to CE, including disposal of complete carcasses and offal, and decreases in fertility and the quality of meat and milk (8). Figure 2 shows the CE infection pathway.

Since an efficient vaccine has not yet been developed, treatment remains the only preventive option for hydatid cyst disease (9). Chemotherapy is the preferred treatment for small, inactive cysts, while surgery is considered the first-line approach for large cysts or those residing in complex anatomical sites (10). Despite the effectiveness of conventional therapy in treating hydatidosis, a range of challenges impair the patient's quality of life. For efficient treatment, early detection of hydatid cysts is essential (9). Unfortunately, access to swift, reliable, and precise diagnostic techniques remains challenging for hydatidosis detection (9, 11). Therefore, recently, considerable attention has been directed toward the use of nanomaterial-based approaches to the detection and treatment of hydatid cysts (9, 12).

The current review aimed to investigate the effectiveness of nanocarriers for the detection and treatment of hydatid cysts. This review begins by providing an overview of nanoparticle (NPs)-based detection of CE. It then discusses recent developments in nanocarriers designed for effective drug delivery to treat CE. Finally, the review addresses the disadvantages and challenges of using drug-loaded nanocarriers for effective treatment.

Hydatidosis diagnosis

Current status of diagnosis

The rapid and accurate diagnosis of parasitic infections is very important (13, 14). Therefore, detecting CE at an early stage is highly recommended. Imaging techniques and detection of serum antibodies or specific CE antigens in serum, urine, and saliva are the main methods of CE diagnosis (11). Ultrasonography (USG) is useful for the detection of abdominal and hepatic CE. Computed Tomography (CT) imaging is useful for detecting infectious cysts or cyst calcification, and Magnetic resonance imaging (MRI) is also valuable for diagnosing multiple cysts and cerebral hydatid cysts (15).

Serological methods for CE diagnosis are enzyme-linked immunosorbent assay (ELISA), immunoblotting, indirect hemagglutination (IHA), and examination of hydatid cyst fluids (HCF)(11, 16). Hydatid cyst fluid-derived antigen 5 (Ag 5), antigen B (Ag B), and their recombinant forms are broadly employed for CE immunodiagnosis (11). Hydatidosis diagnosis approaches are shown in Figure 3.

Nanoparticle-based biosensing platforms for hydatidosis detection

Biosensor-based detection is a quantitative analytical method that offers several advantages, including precise timing and high efficacy (17). NPs-based biosensors (nanosensors) have significantly improved the analytical performance of biosensing, especially their sensitivity and specificity due to the exceptional physicochemical properties of NPs (18). The extensive surface-to-volume ratio of NPs allows efficient target binding, which can lead to the development of ultra-sensitive and multi-parametric biosensors (19).

Jahani *et al.* demonstrated that Ag B-labeled gold NPs (AuNPs) can be used for rapid antibody-based serodiagnosis of CE. The Dot-immunogold staining (Dot-IGS) technique showed that AgB targeted by AuNPs in dilutions of 1.1 and 1.50 elicited the best immune response, suggesting a selective, cost-effective, and simple method that does not require specialized techniques for CE diagnosis (20). In a study to detect human CE using AgB from *E. granulosus* cyst fluid, western blotting showed a specific 8-12 kDa subunit band when using positive serum. The platform showed 95% and 100% sensitivity for IgG4 and IgG, respectively, in real serum samples. For human CE detection, IgG4 had more specificity than IgG, 100% versus 87.5% (21).

An optical-based spectrophotometer-free device using

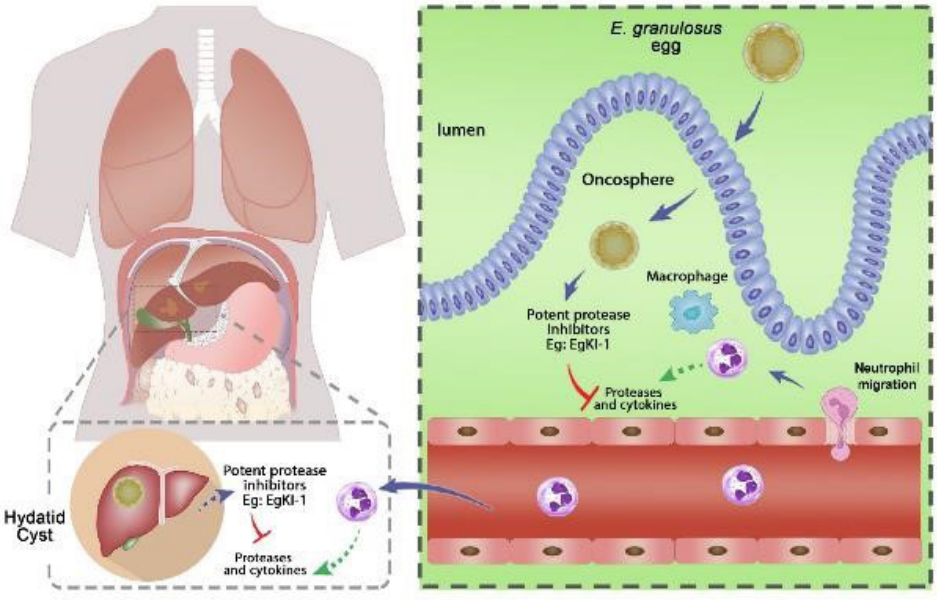

Figure 2. Cystic echinococcosis infection pathway

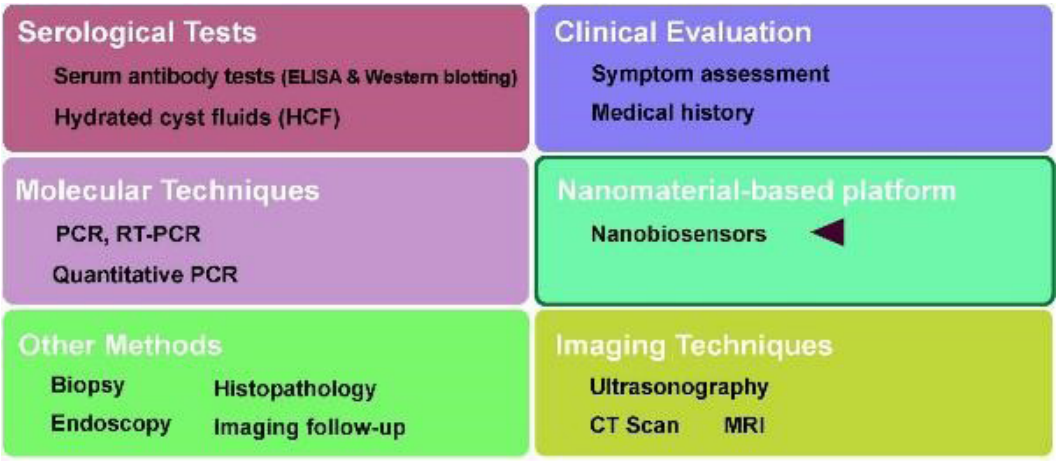

Figure 3. Hydatidosis diagnosis approaches
PCR: Polymerase chain reaction; CT: Computed tomography; MRI: Magnetic resonance imaging

porous silicon micropores detected 43 kDa CE antigens using a label-free, sensitive approach (22). In the same study, when anti-p38-labeled CdSe/ZnS quantum dots (QDs) linked to the Egp38 antigen were used after biological reaction in porous silicon (PSi), enhanced QD fluorescence enabled identification of the Egp38 antigen with a limit of detection (LOD) of 300 fg/ml (23). In 2022, Jafari *et al.* designed a nanobiosensor based on AuNPs with a high sensitivity that specifically diagnosed hydatid cyst with a LOD of 0.001 μg mL^{-1} (24). A NPs-based ELISA designed by the combination of AuNPs with anti-sheep conjugate (AuNPs/nano-ELISA) detected hydatidosis in sheep using AgB with a specificity and sensitivity of about 96% and 100%, respectively (25).

Hydatidosis treatment

Treatment options for hydatidosis are determined by the cyst features and include medical therapy, surgery, and subcutaneous aspiration of PAIR (Puncture, Aspiration, Injection, Re-aspiration) for accessible cysts (5). In humans, surgery is the primary and preferred treatment method for accessible cysts and complete cyst removal. Nevertheless, surgery is not always indicated for cysts in high-risk organs or for multiple lesions in different organs. In addition, there is a risk of disease recurrence due to leakage of protoscolex-rich cyst fluid, and anaphylactic shock may accompany it in certain instances (5, 26). Although PAIR/surgery co-treatment is considered an effective treatment, the use of hypertonic saline as a scolicidal agent during surgery can cause adverse effects such as seizures, intracranial hemorrhage, necrosis, degeneration, and myelinolysis (7).

Drug therapy, especially benzimidazole, is another option, but sometimes takes a long time, and only small and superficial cysts may respond to antiparasitic drugs. Drug treatment may be followed by aspiration or surgery (5).

Chemotherapy

Benzimidazole (1H-benzimidazole/benzoglyoxaline/1,3-benzothiazole) is a bicyclic compound consisting of a benzene ring fused to an imidazole ring bearing two nitrogen atoms (27). Benzimidazoles are highly potent compounds, exhibiting significant inhibitory activity along with a desirable selectivity. A wide range of pharmacological investigations have validated the antiparasitic activity of benzimidazoles (27, 28).

Currently, two benzimidazole derivatives, namely albendazole (ABZ) and mebendazole (MBZ), are used to treat CE disease. These medications cause morphological changes in the cysts, including reduced cyst volume, membrane detachment, and calcification (29). ABZ disrupts tubulin polymerization, leading to the destruction of cytoplasmic microtubules. It also causes destructive changes in the parasite's intestinal wall cells, leading to decreased ATP production and energy depletion, ultimately resulting in the parasite's death (30). These drugs are extremely hydrophobic (Class II BCS) and therefore require high doses and prolonged administration (31). Clinically, ABZ is recommended at 10 mg/kg/day, twice daily with a meal, and co-administration with gastric acid–reducing agents (29).

Unfortunately, the use of benzimidazoles is often limited by numerous side effects, such as impaired liver function, severe leukopenia, hepatotoxicity, thrombocytopenia, alopecia, abdominal pain, diarrhea, nausea, dizziness, and headaches (5). ABZ efficacy is often hindered by poor intestinal absorption, mainly due to its low aqueous solubility, and the use of NPs is considered an effective approach to enhance drug solubility and dissolution (32).

Nanocarrier-based hydatidosis treatment

The disadvantages of chemotherapy include poor bioavailability, high doses, repeated injection, the widespread development of resistance, a low therapeutic index, adverse side effects, and non-specific targeting. Furthermore, the non-selective distribution of drugs may induce severe systemic toxicity in normal organs (33). To transcend these constraints and deliver drugs to the targeted area in the body, advanced nano-based technology is used (33).

The use of NPs can be an alternative option for traditional drug delivery due to their exceptional characteristics, which provide tremendous benefits for drug delivery, including increased effectiveness, higher efficiency, bioavailability, dosage response, improved transport through biological barriers to the intended site, lower toxicity, immunogenicity, long-term blood circulation, and fewer side effects, etc. (33, 34).

In the case of CE, various drug-loaded nanocarriers such as solid lipid NPs (SLNs), liposomes, nanocapsules, and micelles have been developed. Many issues, including

poor solubility of anti-parasite drugs, low absorption, fast drug metabolism and elimination, irregular absorption and release of drugs, high dosages, and low effectiveness, have been solved with nanomaterials-based drug delivery systems (35).

Lipid-based nanostructure for drug delivery

Liposomal system

Among the various delivery systems, liposomes are the most desirable system due to their biocompatibility and high safety (36, 37). Liposomes separate an aqueous medium via two phospholipid layers that encapsulate lipophilic and hydrophilic drugs, protecting the active compounds from degradation while prolonging systemic circulation, enhancing selectivity, and reducing drug-associated side effects (36, 37). A study demonstrated the *in vitro* protoscolicidal efficacy of 2 mg/ml Huaier aqueous extract combined with 10 µg/mL ABZ liposome (L-ABZ). In *E. granulosus*-infected mice, oral treatment with both formula (three times per week for 4 months) showed enhanced efficacy (38). A non-randomized clinical trial indicated that both tablet-ABZ (T-ABZ) and L-ABZ effectively treat human CE. The total effective rates (TERs) for L-ABZ were markedly higher than those achieved with T-ABZ (39). It has also been demonstrated that single and repeated oral doses of 10 mg/kg L-ABZ could increase the concentration and the relative bioavailability of ABZ and its metabolites in sheep infected with *E. granulosus* (40). It has been shown that optimal doses of juglone (5-hydroxy-1,4-naphthoquinone)-loaded nanoliposomes can elevate caspase-3 mRNA expression and exhibit significant scolicidal effects *in vitro* (Figure 4)(41).

The efficacy of the 14-3-3–MPLA–liposome vaccine in conferring high-level protective immunity against CE was confirmed, with 95.07% protection in immunized mice challenged with protoscoleces (PSCs). According to the ELISA assay, the vaccinated mice showed a considerable rise in IgG1, IgG2a, and interferon gamma (IFN-γ) levels (42). Xiong *et al.* created a phototheranostic system that actively targets CE for photothermal therapy and near-infrared fluorescence diagnosis using neutrophil-membrane-coated indocyanine green liposomes (Neu-lipo-ICG). Photothermal therapy mediated by Neu-lipo-ICG dramatically decreased the lesion volume after 7 days, demonstrating that when exposed to near-infrared laser light, Neu-lipo-ICG successfully eradicated hydatids (43). A surfactant-based nanomicelles encapsulated with 0.5, 0.25, 0.125 mg/ml curcumin (CUR) displayed significantly lower total cyst numbers and weight than the CUR, ABZ (150 mg/kg), and negative control groups (44).

Solid lipid nanoparticles (SLNs)

SLNs can effectively deliver hydrophobic drugs and protein and peptide therapeutics. They consist of waxes, triglycerides, glycerides, and solid lipids stabilized by surfactant agents (45). Stability, biocompatibility, prolonged drug release profile, minimal toxicity, and target specificity are just a few benefits of using SLNs (46). These unique size-dependent properties make SLNs a suitable candidate for anti-CE drug delivery.

Jaiswar *et al.* confirmed that chemoprophylaxis treatment of hydatid cysts in mice using ABZ- and praziquantel (PZQ)-encapsulated SLNs resulted in a reduction of 83% and 85% in cyst weight and size, respectively, compared to ABZ and PZQ (77.3%, 79%), suggesting a greater efficiency of ABZ/SLNs and PZQ/SLNs compared to free ABZ and PZQ (47). In a study, ABZ- and ABZ sulfoxide (ABZSO)-encapsulated SLNs produced by microemulsion and high-pressure homogenization increased hydatid cyst membrane permeability, efficiency, and controlled release of ABZ and ABZSO for its treatment. The optimized formulation displayed particle sizes below

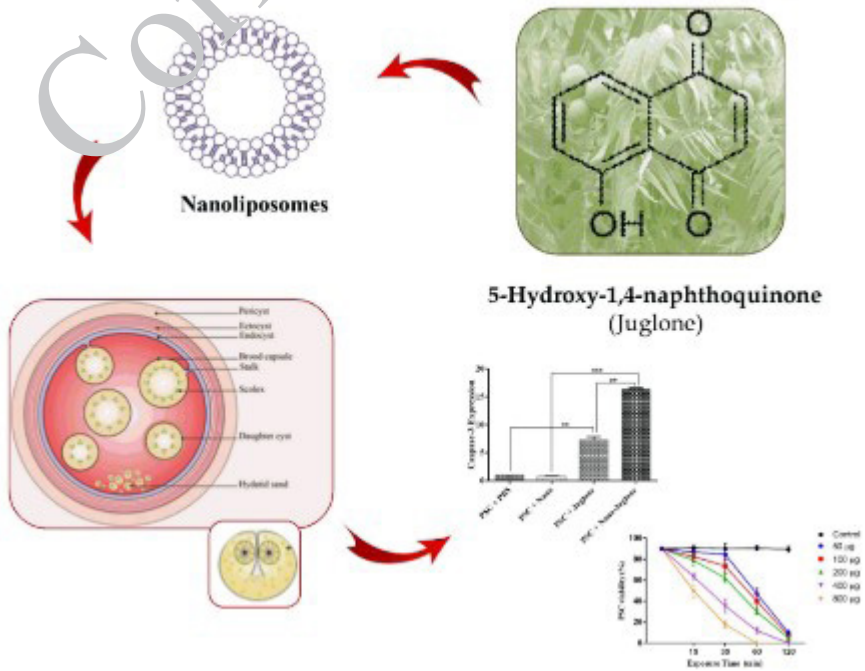

Figure 4. Schematic illustration of a liposomal nanocarriers loaded with juglone as a potent agent against *Echinococcus granulosus* PSCs
Reprinted with permission from (41) published under a CC BY 4.0 license

180 nm, polydispersity indices (PDIs) around 0.08, and entrapment efficiencies (EE%) of about 91% and 94% for ABZ/SLNs and ABZSO-SLNs, respectively (48). Rafiei *et al.* verified the efficacy of ABZ/SLNs and ABZSO/SLNs against fertile and infertile hydatid cysts of sheep liver by examining the ultrastructural changes of the cysts. The light microscope and transmission electron microscope (TEM) showed that ABZ/SLN and ABZSO/SLNs caused more structural changes in small fertile cysts (35).

The *in vitro* protoscolicidal effect of 250 and 500 µg/ml ABZ/SLNs on PSCs cultured in RPMI medium showed the highest lethality on day 5. Autopsy results revealed cyst growth in all mice. In the ABZ/SLNs group, no cysts were observed in only 2 mice, suggesting that ABZ/SLNs may be a preventive measure against the development of CE (49). In a study, nephrotoxicity induced by ABZ and ABZ/SLNs was evaluated in experimentally infected mice. A high-pressure homogenization and micro-emulsification technique was used to produce ABZ-loaded SLNs. A significant difference was observed in levels of blood urea nitrogen (BUN) and pathologic and nephropathic alterations between the control group with ABZ and ABZ/SLNs-received mice. ABZ/SLNs provided superior prophylactic protection against CE, without adverse effects or abnormalities in kidney histopathology or biochemistry, demonstrating ABZ/SLNs as potential carriers for the treatment of CE (50). In a study, during chemoprophylaxis, ABZ/SLN conjugated to albumin (ABZ/SLN-B) showed ultrastructural changes and a significant reduction in the number and weight of cysts, and wet weights of metacestodes in mice compared with free ABZ (51).

Nanostructured lipid carriers (NLCs)

Nanostructured lipid carriers (NLCs) consist of a blend of liquid and solid lipids in varying proportions that have exceptional physicochemical and biocompatible properties (52). They also possess an elevated drug-loading capability and regulated drug release standards, which make them safe and valuable drug delivery systems (52, 53).

A study assessed the apoptotic and cytocidal effects of ivermectin (IVM)-loaded NLCs (IVM/NLCs) versus IVM, a potent nematocidal and anti-parasitic medication, using an *in vitro* assessment of caspase-3 mRNA expression. 100% mortality was observed after administration of 400 µg/ml (120 min) and 800 µg/ml (60 min) IVM-loaded NLCs, whereas the free IVM mortality rate was 800 µg/ml at 150 min. IVM/NLCs, by enhancing caspase-3 mRNA expression, induced a stronger apoptotic effect on the parasite (54). In a mouse model, the effectiveness of human mannose-binding lectin-associated serine protease (hMASP-2)-based immunotherapy against hydatid cysts was investigated using hMASP-2 DNA nanolipoplexes (pcDNA3.1-hMASP-2) and ABZ. Following a six-week course of therapy, significant reductions in cyst weight and a remarkably enhanced number of CD8+T cells, CD4+T cells, and IFN-γ in serum were observed in both groups compared with the untreated group. DNA nano lipoplexes prevented germinal layer growth, leading to widespread destruction, and enhanced T-cell immunity, suggesting a successful therapy for echinococcosis (55). Table 1 summarizes lipid nanocarriers reported for drug delivery in the treatment of CE.

Lipid-based drug delivery challenges for hydatidosis treatment

By reviewing the aforementioned studies, it is evident that liposomal-based formulations, despite their many advantages, have not attracted the attention of researchers

Table 1. Lipid-based nanostructure drug delivery for the treatment of hydatid cyst

Type	Components	Delivery agent	Treatment model	Treatment Time	Dosage	Effect	Ref.
Liposomes/ nanomicelles	juglone (5-hydroxy-1, 4-naphthoquinone) nanoliposmes	juglone	PSCs	15, 30, 60, and 120 min	50, 100, 200, 400, and 800 µg/ml	A rise in the expression of caspase-3 mRNA and scolicidial effects	(41)
	CUR/ABZ nanomicelles	CUR, ABZ	Mice	1 month	CUR: 0.5, 0.25, 0.125 mg/ml ABZ: 150 mg/kg	Reduced cyst weight and number	(44)
SLNs	ABZ and PZQ-encapsulated SLNs	ABZ PZQ	Mice	3 months	ABZ: 50 mg/kg PZQ: 600 mg/kg	Reduced cyst weight and size	(47)
	ABZSO/ SLNs	ABZ ABZSO	PSCs	72 h	5 to 90 µg/l	Enhanced drug efficiency	(48)
	ABZ-SLNs ABZSO-SLNs			72 h	2000 µg/l	Structural changes of cysts	(35)
	ABZ/ABZ-SLNs			7 days	500, and 250 µg/ml	Reduction the number of hydatid cysts	(49)
	ABZ/ABZ-SLNs	ABZ	Mice	4 weeks	200 mg/kg	A more prominent chemoprophylactic efficacy on CE and fewer side effects than ABZ alone	(50)
	ABZ/SLN-albumin	ABZ	Mice	21 days	25 mg/kg	- Structural changes - a significant reduction in the number and weight	(51)
NLC	NLC-loaded IVM	IVM	PSCs	60, 120 and 150 min	400 and 800 µg/ml	A rise in the expression of caspase-3 mRNA	(54)
Lipoplexes	hMASP-2 DNA nanolipoplexes and ABZ	ABZ	Mice	6 weeks	100 mg/kg/day	Suppressing the growth of cysts Enhanced T-cell immunity	(55)

PSCs: Protoscoleces; CUR: Curcumin; ABZ: Albendazole; PZQ: praziquantel; SLNs: Solid lipid nanoparticles; ABZSO: ABZ sulfoxide; NLCs: Nanostructured lipid carriers; IVM: Ivermectin; hMASP: Human mannose binding lectin-associated serine protease

for CE treatment. Several limitations of conventional liposomes, such as poor EE% of hydrophilic drugs, drug leakage through the unstable membrane, a short half-life, low penetration across the skin into deep tissues and blood circulation, and opsonization and immunogenicity, may be among the reasons (56, 57). Additionally, the efficacy of encapsulated medications depends on their release after liposomal disruption (58). Consequently, it is necessary to fine-tune the release rate of liposome-based drug carriers to mitigate premature release and achieve optimal therapeutic efficacy. Using SLNs in anti-CE drug delivery could provide significant benefits, such as biocompatibility and stability, target specificity, sustained drug release, and low systemic toxicity, similar to other SLN-based drug delivery systems (52, 59). Some of the primary drawbacks of SLNs are initial burst release, drug expulsion during storage conditions, and low drug loading (DL) capacity. These drawbacks of SLNs resulted in the development of the next generation of lipid carriers, named NLCs. NLCs are biocompatible, have high drug-encapsulating ability, and, with a regulated drug release pattern, display excellent solubility, permeability, and stability (53).

Polymeric nanoparticles for drug delivery

Polymer-based NPs

Polymeric NPs (PNPs) consist of natural or synthetic polymers that are biocompatible, non-toxic, and biodegradable (52, 60). The natural polymers include alginate, gelatin, chitosan, and albumin, while the synthetic polymers include thermoplastic and thermoset polymers (60). Because of their unique characteristics, such as small size and ability to penetrate through capillaries, PNPs have been extensively utilized in biomaterial applications like imaging, biological sensors, and drug delivery systems (61). This section, along with Table 2, presents a comprehensive overview of PNPs used in CE treatment.

Table 2. Polymeric and nanocrystals (NCs)-based drug delivery for the treatment of hydatid cyst

Type	Components	Delivery agents	Treatment model	Dosage	Treatment Time	Effect	Ref.
Polymeric nanoparticles	FLBZ/ mPEG-PCL NPs	FLBZ	Mice	10, 5, and 1 µg/ml	14 and 27 days	- Significant reduction in the cyst number and weight	(62)
	ABZ/MBZ/ PZQ nanocapsules	ABZ/MBZ/ PZQ	PSCs /Mice	0.25, 0.5, 1 mg/ml	10, 60, 120 min	- A scolicidal activity - Decrease the size, weight, and number	(63, 64)
	Phytase enzyme-targeted PLGA NPs/ABZSO/PZQ	ABZSO/PZQ	PSCs	ABZSO: 10 µg/ml PZQ: 50 µg/ml	4 hrs	- Increase the permeability of drugs *via* laminar layer	(65)
	PAMAM nanoemulsion	PAMAM	PSCs	0.5-2 mg/ml	5, 10, 20, 30 min	- Concentration- and time-dependent anti-PSCs effect	(66)
	DHA-STC-PLGA NPs	DHA	Mice	200 mg/kg	2 days	- Decrease the serum levels of hepatic enzymes	(67)
	ABZSO/CS-PLGA NPs	ABZSO	Mice	10 mg/kg	45 days	- Decrease in the weight and volume of cysts	(75)
	ABZ-linked NPs (ABZ/CS NPs)	ABZ	Rats	50 mg/kg	48 hours	- Exhibits wide distribution and low bioavailability, and low toxicity	(71)
	ABZ/CS NPs PZQ/CS NPs	ABZ/PZQ	Mice	1, 5, and 10 µg/ml	21 days	- Decrease the size and number of cysts	(72)
	CUR-loaded CS NPs	CUR	PSCs	4, 2, 1, 0.25, and 0.05 mg/ml	5, 10, 20, 30 and 60 min	- Enhanced mortality rate - Reduction the weight and size of PSCs	(73)
	ABZ and NSO loaded CS NPs	ABZ and NSO	Mice	1.14 gm/kg	4 months	- A significant increase in IL-5 and NO - A significant decrease in TNF-α	(74)
	CS NPs	CS	PSCs	between 125 and 1000 µg/ml	10, 60, 120, and 180 min	- Highest scolicidal activity	(76)
			Mice	-	-	- Suggesting the CS NPs as a proper adjuvant	(77)
	ZnNPs/CS-camphor/ZnNPs-CS/C	ZnNPs/ABZ	PSCs/Mice	ZnNPs: 10 and 15 mg/ml ABZ: 100 mg/kg	*In vitro*: 10-60 min *In vivo*: 28 days	- Reduction in the size, number, and weight - Reduction in oxidative stress	(78)
	ABZ and NTZ/ CS NPs	ABZ/NTZ	Mice	ABZ: 50 mg/kg NTZ: 200 mg/kg	14 days-4 week	Anti-CE activity	(79)
Nanocrystals (NCs)	ABZ/NCs	ABZ	Mice	25 mg/kg	0.08-24 h	- Improvement of the pharmacokinetic properties of ABZ NCs	(89)
	RBZ-loaded NCs	RBZ	Dog	10 mg/kg	24 h	A notable rise in oral absorption of RBZ	(90)
	ABZ/NCs	ABZ	PSCs	8 mg/ml	5-150 min	Exhibited superior anthelmintic action	(32)
	ABZ/PVP/NCs/ microneedles	ABZ	Porcine skin	15 mg/kg	0.5-72 h	Improve the efficacy of ABZ in CE treatment	(91)
	ABZ/NCs	ABZ/ABZSO/$ABZSO_2$	Rat	100 mg/Kg	0.5-96 h	Enhance the oral bioavailability	(92)
	ABZ/NCs	ABZ	Mice	25 mg/kg/day	30 days	A higher cyst inhibition effect	(93)
	ABZ/NCs	ABZ	PSCs	1 µg/ml	17 and 23 days	A protoscolex inhibition	(94)

FLBZ: Flubendazole; mPEG: Methoxy polyethylene glycol; PCL: Polycaprolactone; ABZ: Albendazole; MBZ: Mebendazole; PZQ: praziquantel; PLGA: Poly lactic-co-glycolic acid; NPs: nanoparticles; ABZSO: ABZ sulfoxide PAMAM: Polyamidoamine; DHA: Dihydroartemisinin; STC: Sodium taurocholate; CS: Chitosan; CUR: Curcumin; NO: nitric oxide; NSO: Nigella sativa oil; IL-5: Interleukin 5; TNF-α: Tumor necrosis factor alpha; CE: Cystic echinococcosis; NCs: Nanocrystals; NTZ: Nitazoxanide; RBZ: Ricobendazole; PVP: Poly(vinylpyrrolidone); ZnNPs: Zinc NPs; PSCs: Protoscoleces; ABZSO2: ABZ sulfone

In a study, the chemoprophylactic effect of flubendazole (FLBZ)-encapsulated methoxy polyethylene glycol-polycaprolactone (mPEG-PCL) NPs and free FLBZ at 1, 5, and 10 µg/ml concentrations was investigated in mice infected with *E. granulosus* cysts and PSCs for 14 and 27 days. The FLBZ-loaded NPs were stable for 1 month with a DL% and EE% of about 3% and 89%, respectively. After 7 days of exposure, mPEG-PCL NPs loaded with 10 µg/ml FLBZ induced 100% mortality of PSCs and elimination of microcysts, while 44.0% of PSCs survived after exposure to 10 µg/ml free FLBZ. *In CE-infected mice,* FLBZ-loaded NPs reduced cyst number and cyst weight, with effectiveness rates of 94.64% and 70.21%, respectively (62).

Soleymani *et al.* demonstrated that among polymeric nanocapsules loaded with 1, 0.5, and 0.25 mg/ml of ABZ, MBZ, and PZQ, as single or multiple, at 10, 60, and 120 min, the ABZ/MBZ co-loaded formulation exhibited the highest scolicidal activity at a concentration of 1 mg/ml after 120 min. In addition, the combination formulations of ABZ, MBZ, and PZQ significantly reduced the size, weight, and number of hydatid cysts in the mice model (63, 64). Phytase enzyme-targeted poly lactic-co-glycolic acid (PLGA) NPs loaded with 10 µg/ml ABZSO and 50 µg/mL PZQ caused a 100% lethality of hydatid cyst on day 4, versus a 50% death rate for the combination of the same amount of drug. These NPs increased the permeability of ABZSO and PZQ through the laminar layer of hydatid cysts isolated from sheep liver almost 2-fold (65). A concentration- and time-dependent anti-PSCs effect of polyamidoamine (PAMAM) nanoemulsion (0.5-2 mg/ml) was observed at different exposure times (5, 10, 20, and 30 min). Camel-based PSCs displayed complete damage to tegument integrity, rostellar hooks, and disruption of suckers, with disorganization of hooks after treatment with the improved formulation (66). To enhance non-specific biodistribution and low bioavailability of Dihydroartemisinin (DHA) as a potent anti-CE, a DHA-loaded PLGA NPs modified with sodium taurocholate (STC) named as DHA-STC-PLGA NPs (DSP NPs) notably decreased liver, spleen, and vesicle weights compared to ABZ-treated mice. Moreover, the serum levels of hepatic enzymes, interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and interleukin 10 (IL-10) were significantly decreased in the DSP NPs group (67).

Chitosan-based NPs

Chitosan (CS) is known as a valuable chitin derivative and an abundant biopolymer after cellulose. CS is made of chitin found in insect exoskeletons, the shells of marine species, including shrimp or crabs (68). CS is a linear polysaccharide made up of randomly dispersed D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). CS is a non-toxic, biocompatible, and biodegradable polymer for tissue engineering and targeted drugs/gene delivery (69, 70).

Liu *et al.* prepared ABZ-conjugated CS NPs (ABZ-CS-NPs) by an emulsion cross-linking volatile method using sodium tripolyphosphate as the cross-linking agent and Poloxamer 188 (P188) as a surfactant to improve the treatment of helminthic diseases. In this line, ABZ/CS NPs showed efficient EE%, extended drug release, and enhanced relative bioavailability values of ABZ to 146% and ABZ-SO to 222%, introducing a passive diffusion mechanism for ABZ to treat liver CE (71). *In vitro* evaluation of ABZ/CS NPs and CS/PZQ NPs on hydatid microcysts demonstrated superior efficacy compared to the free ABZ+PZQ suspension. In prophylaxis, ABZ/CS NPs and CS/PZQ NPs markedly reduced cyst size and count, but in the treatment setting, only cyst count decreased (72).

In a study, among various amounts (4, 2, 1, 0.25, and 0.05 mg/ml) of CUR-loaded CS NPs, the amount of 4 mg/ml of CUR/CS NPs had the best scolicidal activity with a mortality rate of 68%, and reduced the PSCs, suggesting the CUR/CS NPs as an anti-PSCs agent (73). Kishik and his colleagues used CS NPs to boost the effectiveness of *Nigella sativa* oil (NSO) in combination with ABZ for CE treatment. A significant increase in the average level of nitric oxide (NO) and the plasma levels of IL-5 and a remarkable decrease in the systemic level of TNF-α were determined in the CE-infected mice receiving ABZ/NSO-loaded CS NPs compared to the untreated control group (74). In a study, ABZ-SO-encapsulated CS-PGLA NPs synthesized *via* nanoprecipitation were evaluated in CE treatment in experimentally infected mice at a daily dose of 10 mg/kg. Despite no statistical difference in the therapeutic outcomes of ABZ-SO/CS-PLGA NPs and free ABZ-SO, CS-PGLA NPs encapsulated with ABZ-SO were able to increase the therapeutic efficiency of ABZ-SO in CE treatment (75).

The synthesized CS NPs at concentrations ranging from 125-1000 µg/ml exhibited cytotoxic and scolicidal activity. CS NPs reached their highest scolicidal activity at 1000 µg/mL after 180 min, confirming the potential of a lower dosage of CS NPs as a very effective and safe scolicidal agent (76). A bioinformatic-based multi-epitope canine-targeted anti *E. granulosus* vaccine candidate based on CS NPs as adjuvants and four *E. granulosus* antigens, namely, EgM9, EgA31, Eg10196, and EgG1Y162, confirmed CS-NPs as a safe and potent adjuvant for an anti-*E. granulosus* multi-epitope vaccine in dogs (77). In a study, zinc NPs (ZnNPs)-encapsulated CS-camphor (ZnNPs-CS/C) at 10 and 15 mg/mL achieved 100% mortality in PSCs and reduced the size, number, and weight of hydatid cysts in mice. ZnNPs/CS/C in combination with 100 mg/kg ABZ led to a significant enhancement of caspase-3, glutathione peroxidase (GPx), and superoxide dismutase (SOD) activity, and a reduction in oxidative stress, the expression of TNF-α, nuclear factor kappa B (NF-κB) p65, toll-like receptor 4 (TLR4), and interleukin-1beta (IL-1β) genes, demonstrating anti-CE potential of ZnNPs/CS-C/ABZ (78). Recently, a study confirmed that CS NPs could boost the therapeutic efficacy of ABZ and Nitazoxanide (NTZ) in the treatment of CE, as well as the survival time of treated mice. ABZ/CS NPs (50 mg/kg/4 weeks) showed higher anti-CE activity relative to NTZ/CS NPs (200 mg/ kg /14 days) (79).

Polymer-based drug delivery challenges for hydatidosis treatment

Rising stability, non-immunogenicity, and regulated/sustained drug release are the main advantages of PNPs (80). The main challenge in preparing PNPs is finding the most efficient polymer, given their hydrophobicity and hydrophilicity. Other complexities of PNPs are polymer cytotoxicity, utilization of organic solvents in the preparation process, intercellular trafficking, polymer–cell membrane interaction, and the potential to induce autophagy, which can be clarified (80, 81). Hybrid PNPs combined with polymers with natural or synthetic origin may address the

main issues of PNPs (82).

As abovementioned, CS NPs are commonly used PNPs for CE treatment. Two key factors affecting CS-based NPs' performance are the molecular weight (MW) and the degree of acetylation (DA). MW and DA may influence the CS NPs characteristics, such as their solubility, viscosity, temperature transitions, chain length, crystallinity, and tensile strength (83, 84). The interaction of CS biomaterials and human blood is another significant issue that requires hemocompatibility. CS modification and its hybrids with various polymers/lipids/polysaccharides generate hemocompatible CS-based nanocarriers (68, 85).

Nanocrystals (NCs)-based drug delivery systems

Nanocrystallization represents an efficient carrier-free delivery system for enhancing the solubility and bioavailability of poorly soluble drugs (86). This process results in the formation of stable nanocrystals (NCs) when polymers or surfactants are employed to stabilize them under physiological conditions. NCs, in turn, improve the bioavailability and therapeutic efficacy of low-solubility drugs (86, 87). NCs are essential for drug administration because they have the following advantages: (i) higher therapeutic drug concentration at the site of application; (ii) scalable manufacturing processes; (iii) solubilization without extreme pH or co-solvents; (iv) enhanced solubility, adhesion, and dissolution rate; and (v) high content of pure drug with minimal surfactants stabilization (88).

The low aqueous solubility of ABZ and Ricobendazole (RBZ) limits dissolution and absorption in the gastrointestinal tract, potentially reducing their effectiveness. This can be addressed by an NC-based formulation. Compared to the ABZ, the pharmacokinetic performance of ABZ-loaded NCs with a solids yield of 72.32% and a mean particle size of ~ 415 nm was remarkably improved in a mouse model (89). In the same work, RBZ-loaded NCs prepared by an optimized bead milling and spray drying process showed better pharmacokinetic properties in dogs in comparison with a micronized RBZ (mRBZ). RBZ-NCs had a particle size of about 181 nm and displayed a notable rise in oral absorption and a 1.9-fold higher $AUC_{0-\infty}$ in RBZ/NCs-treated dogs versus mRBZ (90).

NCs of ABZ created using the antisolvent precipitation method and spray drying revealed a faster dissolution, crystallinity, lower melting point, and enthalpy, and superior anthelmintic action when compared to pure ABZ (32). In one study, dissolving microneedles (DMNs) were used to intradermally deliver ABZ-loaded NCs stabilized with Pluronic F127, producing NCs with a size of ~400 nm with uniform particle distribution. Dermatokinetic studies across excised neonatal porcine skin with NCs/poly(vinylpyrrolidone)/PVP-based DMNs revealed that over 25% of ABZ persisted within the dermal layer for up to 48 h post-administration. ABZ delivered *via* NCs-loaded DMNs exhibited significantly higher AUC and relative bioavailability (>100%) than either oral formula of ABZ suspension or ABZ/NCs, suggesting a better therapeutic effect of ABZ/NCs/DMNs against CE by bypassing hepatic first-pass metabolism (91). In another study, the prepared ABZ NCs, ABZSO NCs, and ABZ sulfone-loaded NCs ($ABZSO_2$) enhanced oral bioavailability in rats about 1.40 times higher than that of native ABZ (92).

A new ABZ/NCs provided by spray-drying ABZ with P188 improved the oral bioavailability, the drug dissolution performance, and pharmacokinetics of ABZ compared to the commercial oral ABZ (Albenda)(Figure5, Table 2). Oral delivery of ABZ/NCs showed a 3.7-fold cyst inhibition effect in rats, higher than that of ABZ, after 30 days, indicating ABZ/NCs as improved anti-AE drug therapy (93). Fateh and his colleagues also revealed that 1 µg/ml of ABZ/NCs and ABZ completely inhibited the PSCs' survival for 17 and 23 days, respectively (94).

Metal-based nano drug delivery systems

Metal nanomaterials, like zinc oxide (ZnO), iron (Fe), silver (Ag), and gold (Au), can be suitable options for drug delivery.

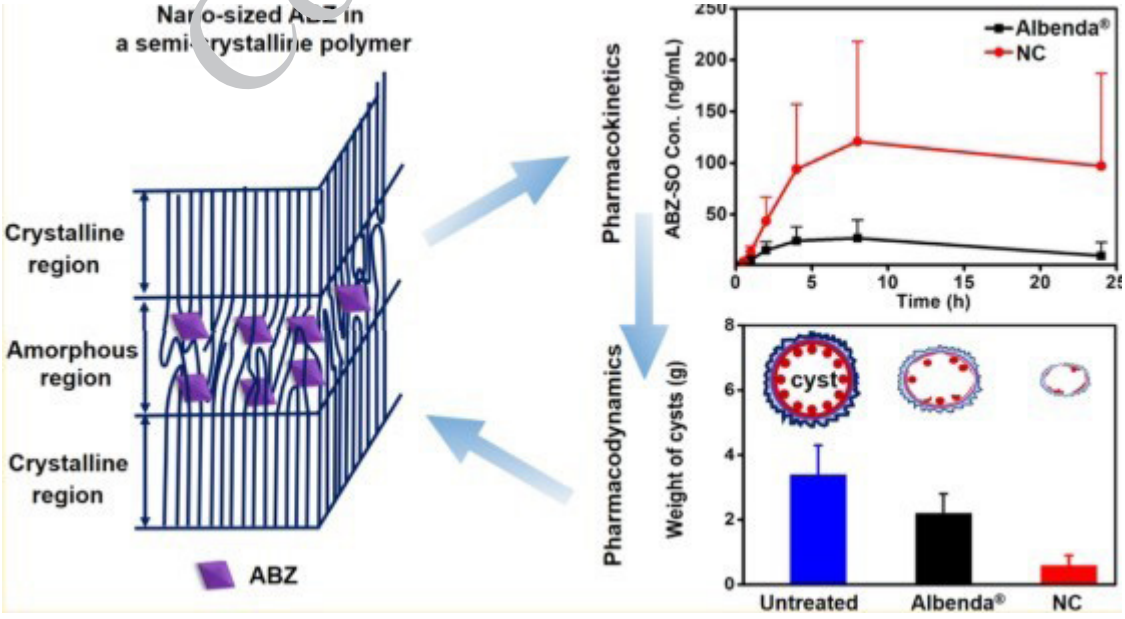

Figure 5. Schematic diagram of nanocrystalline formulation of albendazole (ABZ)(ABZ/NCs) for the treatment of hydatid cyst
Reprinted with permission from Hu *et al.*, Copyright © 2020 American Chemical Society

Magnetic nanoparticles

Magnetic NPs (MNPs) or superparamagnetic iron oxide NPs (Fe_3O_4/SPIONs) can be used as delivery and imaging agents due to their ease of operation, attractive manipulation, and energy-transfer ability (95). However, it is necessary to modify the surface of MNPs to avoid the toxicity, instability, and aggregation of bare MNPs at physiological pH (70).

MNPs are carriers for efficient ABZ delivery (Table 3). A multifunctional ultrasound core/shell-based mesoporous magnetic SLNs composed of SPION as the core and stearic acid as the shell displayed a uniform spherical shape with minimal surface aggregation. The *in vitro* release of ABZ reached 84% gradually within 36 h, highlighting a fast and highly efficient method for ABZ delivery (96). The magnetic microspheres are regarded as drug carriers when guided by an external magnetic field. In a study, the treatment of mice infected with *E. multilocularis* by magnetic microspheres loaded with PLGA-Fe-E2-a revealed a substantial decline in the parasite load, a significant rise in the level of IFN-γ, and morphological and ultrastructural disorders similar to protoscolicidal of ABZ (97).

Critical note: Magnetic NPs present many interesting characteristics, like attractive manipulation and easy functionalization that can be used in delivering drugs (95). However, surface modification of these NPs is essential, since uncoated Fe_3O_4 NPs are prone to aggregation, instability under physiological pH, and protein corona with the plasma proteins (70). Conjugation of SPION with anti-CE targeting antibodies and loaded with ABZ may offer a potential platform for the targeted ABZ delivery and effective AE and CE therapy.

Gold nanoparticles (AuNPs)

Because of their unique optical properties, hydrophilicity, monodispersity, high surface-to-volume ratio, and low toxicity, AuNPs are emerging as a viable drug delivery method (98). The photothermal effect of AuNPs can increase the temperature of the cyst media and kill the surrounding PSCs (99). Table 3 provides the reported AuNPs-based drug delivery for the treatment of hydatid cyst.

Some studies confirmed that AuNPs are an efficient scolicidal agent, since an increase in PSCs mortality was obtained with increasing AuNPs dose or exposure time. Barabadi and colleagues demonstrated a significant scoliocidal activity of different concentrations of 0.05-0.3 mg/mL of *Penicillium aculeatum*-based green-synthesized AuNPs against cystic hydatid and *E. granulosus* PSCs. The highest scolicidal effect of AuNPs was at 0.3 mg/ml and an exposure time of 120 min, with an average removal ratio of 94% (100). In a similar study, significant scolicidal effects of AuNPs at 0.25, 0.5, and 1 mg/ml were observed at 5, 10, 20, 30, and 60 min. The 1 mg/ml AuNPs concentration eliminated all PSCs within 60 min (101). Another study investigated the significant scolicidal effects of 1-5 mg/ml AuNPs, with 76% killing for 4 mg/mL AuNPs for 60 min (102). Çolak *et al.* assayed the photothermal-based scolicidal effects of 0.8 and 0.4 ml of AuNPs along with laser powers of 150, 50, and 30 mW for 30-120 min. In the high-dose AuNPs group at 150 mW laser power for 120 min, 89.30% mortality of PSCs occurred, demonstrating the anti-CE potential of AuNPs/laser irradiation (99). AuNPs biosynthesized using the aqueous extract of the aerial parts of *Salvia sclarea* L. indicated the highest lethality (100%) of PSCs at the concentration of 320 µg/ml after 15 min (103).

Critical note: AuNPs with significant changes in size, ultrastructural modifications of the shell and sucker, as well as the fragmentation of the parasite's DNA, can act as scolicidal agents against CE PSCs and be effective in CE therapy (99, 102). Although AuNPs have gained promising benefits, they have some important disadvantages, such as the formation of a dynamic NPs-protein corona and hyperthermia as a side effect (98).

Zinc oxide nanoparticles (ZnO NPs)

ZnO NPs are a metal oxide, Food and Drug Administration (FDA)-approved food additive. ZnO NPs

Table 3. Magnetic and AuNPs-based drug delivery systems for the treatment of hydatid cyst

Type	Components	Delivery agents	Treatment model	Dosage	Treatment Time	Effect	Ref.
Magnetic nanoparticles	ABZ-SLNs and magnetic SLNs	ABZ	PSCs	-	36 hours	A faster and high-efficiency synthesis method for ABZ delivery	(96)
	Magnetic microspheres loaded with E2-a (PLGA-Fe-E2-a)	E2-a (PLGA-Fe-E2-a)	Mice	- ABZ: 100 mg/kg/day - E2-a: 50 mg/kg/day - PLGA-Fe-E2-a: 50 mg/kg/3 day	6 weeks	A significant rise in the level of IFN-γ Inhibiting metastases growth	(97)
Gold nanoparticles (AuNPs)	Green synthesis of AuNPs using *P. aculeatum* extract	AuNPs	PSCs	0.3, 0.2, 0.1 and 0.05 mg/ml	10. 30. 60, and 120 min	A potential scolicidal agent for CE	(100)
	AuNPs			0.25, 0.5, and 1 mg/ml	5, 10, 20, 30, and 60 min	Significant scolicidal effects	(101)
	AuNPs			1-5 mg/ml	5, 10, 20, 30, and 60 min	- Significant changes in size, structure and shape of the sucker - The fragmentation of the parasite's DNA	(102)
	AuNPs/laser irradiation			0.8 and 0.4 ml	30, 60, and 120 min	- An increase in protoscolicidal mortality	(99)
	Green synthesis of AuNPs using *S. sclarea* extract			320 µg/ml	15 min	A highest lethality	(103)

ABZ: Albendazole; SLNs: Solid lipid nanoparticles; PSCs: Protoscoleces; AuNPs: Gold NPs; CE: Cystic echinococcosis.

are recognized as a valuable and versatile compound due to their chemical stability, broad-spectrum radiation, elevated electrochemical coupling, and superior photostability (104). ZnO NPs are safe and non-toxic in low concentrations and exhibit notable antimicrobial capabilities due to their nano size (104, 105). Some research has also reported the anti-CE effect of ZnO NPs (Table 4).

The *in vitro* evaluation of scolicidal effect of 50, 100, and 150 mg/ml ZnO NPs on PSCs at 10, 30, and 60 min displayed that 50 mg/mL ZnO NPs led to 6.19% elimination at 10 min, while 150 mg/ml killed all PSCs (106). Mahmmoud *et al.* investigated 100 µg/ml ZnO NPs and 1000 mg/ml of aqueous extracts of grape seeds, which have a deadly effect on PSCs isolated from sheep liver hydatid cyst (107). In a study, 200 µg/ml green synthesized ZnO NPs by *Lavandula angustifolia* extract showed the highest protoscolicidal effects *in vitro* at about 81.6%. Moreover, ABZ (100 µg/ml)-loaded ZnO NPs completely killed the PSCs at 10 min, suggesting ZnO NPs/ABZ as a strong protoscolicidal agent (108). The green synthesized ZnO NPs from *Mentha longifolia L.* leaf extract at a concentration of 400 ppm for 150 min showed the highest protoscolicidal activity with

Table 4. ZnO NPs and AgNPs-based drug delivery systems for the treatment of hydatid cyst

Type	Components	Delivery agents	Treatment model	Dosage	Treatment Time	Effect	Ref.
Zinc oxide NPs (ZnO NPs)	ZnO NPs	ZnO NPs	PSCs	50-150 mg/ml	10, 30, and 60 min	A significant protoscolicidal activity	(106)
	ZnO NPs and the aqueous extracts of grape seeds	ZnO NPs/ grape seeds	PSCs	250, 500, and 1000 mg/ml	5, 10, 15, 30, and 60 min	A higher mortal rate	(107)
	Green synthesized ZnO NPs by *L. angustifolia* extract		PSCs	200, 100, and 50 µg/ml	0-60 min	A strong protoscolicidal effect	(108)
	Biosynthesized ZnO NPs prepared with *M. longifolia* extract		PSCs	100, 200, and 400 ppm	150 min	- A highest scavenging activity with a mortality rate of 100%. - An effective scolicidal potential	(109)
	Salicylate-coated ZnO NPs	Salicylate	PSCs	1500, 2000 µg/ml	0-30 min	- Activation of Caspase-3&7 Morphological changes including tegument surface wrinkles and apoptogenic changes	(110)
	ZnO NPs and ZnO/Brt/CS nanocomposites extracted from *T. ammi*		PSCs	200 mg/ml	30-60 min	100 % lethal	(111)
	linalool-ZnO nanocomposite (Lin-ZnNPs)/PVA		PSCs/ Mice	PSCs: 145-1050 µM Lin-ZNP: 0.11, 0.22, 0.44 mol/kg	*In vitro*: 5-60 min *In vivo*: 28 days	A dose- and time-dependent death	(112)
Silver NPs (AgNPs)	AgNPs amphotericin B, *F. vulgare* Mill, hypertonic saline, and essential oil		PSCs	AmB: 20-2.5 µg/ml, Ag-NPs: 0.5-4 mg/ml, *F. vulgare* oil 1-0.125 mg/ml	5-60 min	Strong scolicidal activity	(113)
	Green synthesized AgNPs from aqueous extract of *P. aculeatum*		PSCs	0.15, 0.1, 0.05, and 0.025 mg/ml	10-120 min	- High scolicidal effects	*(114)*
	green synthesis of AgNPs using *Z. spina-christi* leaves		PSCs	0.05, 0.1, 0.2, 0.3 and 0.4 mg/ml	10-210 min	Suggested a biocompatible agent for CE treatment	(115)
			Mice	300 mg, 200 mg, 100 mg, and 50 mg/kg	14 days	Proposed an anti-echinococcal cyst therapy	(116)
	AgNPs free or mixed with ABZ	AgNPs/ABZ	Mice	400 mg/ 10 ml	2 months	Decrease of cyst size and weight	(117)
	AgNPs loaded with ABZ/MBZ	ABZ/MBZ	Mice	3.75 mg/ml	12 weeks	A significant reduction in body weight, liver, spleen, and the number of cysts	(118)
	AgNPs encapsulated with ABZ	core-shell ABZ	PSCs	50, 125, 250, and 500 µg/ml	10-60 min	A strong protoscolicidal effect	(119)
	Green-synthesized AgNPs using *A. spinosus* extract		PSCs/ Mice	25-200 µg/ml 25, 50, 100 mg/kg	*In vitro*: 5-60 min *In vivo*: 4 weeks	- Disrupted the membrane integrity - Enhanced the expression of caspase-3/9 and antioxidant genes	(120)
	Green-synthesized AgNPs using the extract of *D. mucronata* seeds and *S. sclarea*		PSCs	80-320 µg/ml	15 min	100% lethality of CE	(121, 122)
	AgNPs, Ag/Bhm NC using *R. officinalis* extract		PSCs	1.6 mg/ml	60 min	Higher mortality rate	(123)

ZnO NPs: Zinc oxide nanoparticles; ZnO: Zinc oxide; PSCs: Protoscoleces; Brt: Barite; CS: Chitosan; CE: Cystic echinococcosis; Lin: Linalool; ZnNPs: Zinc NPs; PVA: Polyvinyl alcohol; AgNPs: Silver NPs; ABZ: Albendazole; MBZ: Mebendazole; Bhm NC: Boehmite nanocomposite; NC: Nanocomposites

a mortality rate of 100% (Figure 6a)(109). In a study, the synthesized salicylate-coated ZnO NPs (SA/ZnO NPs) at a 2000 µg/ml concentration exhibited 100% PSC mortality at 20 min, compared with free SA and ZnO NPs (Figure 6b). Activation of Caspase-3 & 7 enzymes at 2000 µg/ml was 16.4% for SA/ZnO NPs, 31.4% for ZnO NPs, and 35.7% for free SA (110).

At a concentration of 200 mg/ml ZnO NPs and ZnO/barite/CS nanocomposites (ZnO/Brt/CS NC) produced using aqueous extract of the *Trachyspermum ammi* plant, a 100 % lethal rate was observed in 60 min and in 30 min, respectively (111). The linalool-ZnO nanocomposite (Lin-ZNP) synthesized using an ethanolic solution of polyvinyl alcohol (PVA), significantly killed the PSCs in a dose- and time-dependent manner. Treatment with Lin-ZNP led to a notable depletion in the number, diameter, and weight of the hydatid cysts and a significant increase in the expression of antioxidant genes (112).

The abovementioned ZnO NPs-based approaches exhibiting concentration-dependent enhancement of protoscolicidal effects are not suggested as a strong scolicidal agent (106). ZnNPs in combination with ABZ have been shown to exert a strong protoscolicidal effect when administered intraperitoneally for the treatment of cystic hydatid. However, for use in the clinical environment, more studies are needed to evaluate its effectiveness and safety (108).

Silver NPs (AgNPs)

In some studies, the scolicidal effects of green-synthesized AgNPs have been assessed for inactivating PSCs during hydatid cyst surgery to prevent recurrence and improve blood compatibility (Table 4).

The scolicidal effects of varying concentrations of Ag-NPs, amphotericin B (AmB), and *Foeniculum. Vulgare essential oil* and hypertonic saline were investigated on PSCs extracted from sheep and goat livers for 5-60 min. Maximum mortality was observed at 20 mg/ml AmB (82.3%), 4 mg/mL Ag-NPs (71.6%), 1 mg/ml *F. vulgare* oil (100%), and 20% hypertonic saline (100%). The strong scolicidal activity of the essential oil of *F. vulgare* in combination with AgNPs could be proposed as a novel scolicidal medication for CE

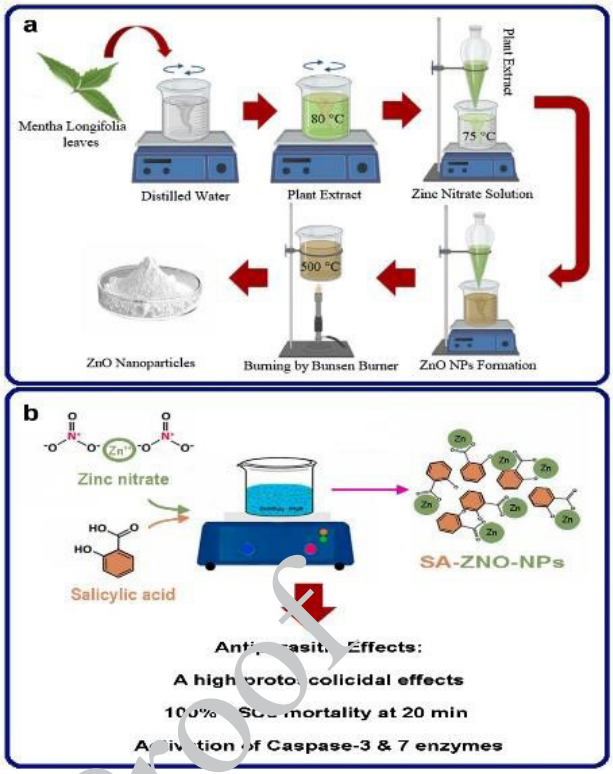

Figure a) Green synthesized ZnO NPs from *Mentha longifolia* L. leaf extract for the assessment of protoscolicidal scavenging activity, reprinted with permission from Shnawa *et al*., published under a CC BY 4.0 license. b) The process of salicylate-coated ZnO NPs and their protoscolicidal activity
ZnO NPs: Zinc oxide nanoparticles. SA: Salicylic acid

therapy (113). *In a study, the* highest *PSCs* mortality rate, about 83% and 90% were obtained from 0.1 and 0.15 mg/ml *green synthesized* AgNPs from *the aqueous extract of P. aculeatum* after 120 min, while 0.025 mg/ml AgNPs in 10 min showed the lowest scolicidal activity (~40%)(114).

In a study, the strong effectiveness of varying dosages of green biosynthesized AgNPs from *Ziziphus spina-christi in inducing morphological changes in E. granulosus* PSCs during hydatid cyst surgery was confirmed (Figure 7)(115).

Figure 7. Green-synthesized AgNPs using Zizyphus spina-christi leaves for the assessment of protoscolicidal effect during hydatid cyst surgery
Reprinted with permission from Jalil et al., published under a CC BY 4.0 license
gNPs: Silver nanoparticles; AgNO3: Silver nitrate

The anti-CE activity of these AgNPs at 50-300 mg/kg was demonstrated in BALB/c mice without adverse effects, symptoms, or mortality. However, mice receiving AgNPs exhibited minor histological changes in the kidneys, liver, and intestines (116). Based on these studies, AgNPs can be considered as scolicidal agents with more efficacy and minimal side effects during the surgery of cystic hydatid.

The anti-hydatidosis effects of AgNPs in combination with ABZ have been another approach. In this line, Nassef *et al.* reported the highest efficacy rate (63.9%) along with ultrastructural changes in cysts and a significant decrease in cyst size, cyst weight, and IFN-γ levels in CE-infected mice after treatment with ABZ-loaded AgNPs (117). In the same study, a significant reduction in body weight, liver, spleen, and the number of cysts in male albino mice experimentally infected with cystic hydatid was obtained after exposure to ABZ/AgNPs and MBZ/AgNPs (118). The results of a study revealed a pronounced mortality rate of PSCs in accordance with increasing the concentration and duration of exposure to Ag-copper NPs and AgNPs-loaded with ABZ (119).

Baghdadi *et al.* reported a dose- and time-dependent scolicidal effect of the green-synthesized AgNPs using the precipitation method with *Astragalus spinosus* extract. AgNPs disrupted the membrane integrity, reduced the size, number, and weight of hydatid cysts, and enhanced the expression of caspase-3/9 and antioxidant genes. Moreover, a notable decrease in the level of IL-4 and IL-10 was detected following AgNP treatment (120). The green-synthesized AgNPs using the extract of *Daphne mucronata* seeds and *Salvia sclarea* flower extract led to 100% lethality of CL in 15 min at the concentration of 80 µg/ml and 320 µg/mL, respectively (121, 122). AgNPs, phytosynthesized Ag boehmite nanocomposite (Ag/Bhm NC) using *Rosmarinus officinalis* extract, exhibited 65.34 % and 51.60 % mortality rate at 1.6 mg/ml and 60 min, respectively (123).

Selenium, copper, TiO_2, NiO, and CeO_2 nanoparticles

Selenium NPs (SeNPs)

Strong scolicidal effects of SeNPs have been reported in some studies. It has been shown that SeNPs affect the survival of *E. granulosus* PSCs by increasing the exposure time. Mahmoudvand *et al.* reported the scolicidal effect of *Bacillus spp.* originated green biosynthesized SeNPs at concentrations of 500 and 250 µg/ml after 10 and 20 min, respectively (124). In comparison between AgNPs and SeNPs at the same concentration (50-500 µg/ml), the protoscolicidal effect of SeNPs on cystic hydatid PSCs isolated from infected sheep (liver and lungs) was remarkably more than AgNPs at exposure times of 10, 20, 30, and 60 min (125). In albino *Mus musculus* mice treated with 150 µg/ml SeNPs, the survival decreasing rate was 90%, while no cysts were formed in mice treated with 200 µg/ml SeNPs, 3 and 4 months after infection (126).

Copper NPs (CuNPs)

Ezzatkhah *et al.* investigated the antiparasitic effects of *250, 500, and 750 mg/ml* green CuNPs synthesized from *C. spinosa* extract alone and combined with *200 mg/ml* ABZ on hydatid cyst PSCs (5-60 min) *in vitro* and *in vivo.* The 750 mg/ml CuNPs showed the highest scolicidal activity, killing 73.3% of PSCs after 60 min, whereas 100% was achieved with CuNPs/ABZ after 10 min (10). In a study, upon administration of 80 mg/kg green-synthesized CuNPs using *Lupinus arcticus* extract for 28 days on hydatid cyst-infected mice, a remarkable decrease in hydatid cysts' size, weight, and number, oxidative stress markers, and inflammatory cytokines was observed (127). The evaluation of the scolicidal and apoptotic effects of Cu oxide (CuO) and gamma alumina (γ-Al_2O_3) with or without CS, using *Rosmarinus officinalis* extract on PSCs, revealed the highest scolicidal effect (33.26 %) by 1.6 mg/mL CuO at 60 min, followed by phytosynthesized CuO/γ-Al2O3 NC (23.41 %) by inducing apoptosis (128).

Titanium oxide (TiO_2) and zirconium oxide (ZrO_2) NPs

A study found that using *Echinometra mathaei* gonad extracts with TiO_2 NPs killed 84% of PSCs after 60 min of incubation at a concentration of 15 µg/ml. Moreover, the reduction in cyst volume, size, and number was observed in mice infected with *E. granulosus* PSCs (129). Two similar studies evaluated the efficacy of 250, 500, 1000, 2000, and 4000 µg/ml TiO_2 NPs and ZrO_2 NPs in treating hydatid cyst PSCs for different times of 15, 30, and 60 min (130, 131).

Nickel oxide (NiO) and Cerium oxide (CeO_2) NPs

In a study, a strong dose-dependent scolicidal activity was obtained by NiO NPs derived from *Ziziphus spina-christi* L. leaves extract due to its simplicity, compatibility with the environment, availability, and non-toxicity during production (Figure 8). The NiO NPs also had strong antioxidant capacity and low hemolytic effect on red blood cells (132).

Aryamand and colleagues assessed the effectiveness of CeO_2 NPs, *Holothuria leucospilota* extract, ABZ, and a mixture of the tree as scolicidal agents against cystic hydatid PSCs in vitro and in vivo over 10-60 min. After 60 min, *H. leucospilota* extract (20 mg/mL) and a CeO_2 NPs/*H. leucospilota* mixture (15 mg/ml) effectively killed PSCs by increasing caspase 3 activity and diminishing cyst count, size, and volume (133).

A summary of Selenium, copper, TiO_2, NiO, and CeO2 NPs for CE treatment has been provided in Table 5.

The main issues of nano drug delivery challenges for hydatid cyst

Nanotechnology may enhance treatment approaches and diagnosis techniques by offering more accurate NPs-based solutions. Nanobiosensors may aid in earlier and more precise diagnosis of hydatidosis. Moreover, hydatid cysts may be successfully treated with nanoformulations, but there are some challenges (9).

This review has addressed recent developments in nanocarriers designed for successful drug delivery to CE. In this context, various NPs, including lipid-based NPs, PNPs, NCs, and metal-based NPs, have been developed. This review showed that the metallic NPs and CS-based NPs were the most commonly used NPs for CE treatment. Moreover, NCs are another nanoformulation reported for this purpose.

However, there are some main challenges, toxic effects, and other unexpected drawbacks associated with nanotherapeutics. It is important to note that the nanocarrier-based delivery is highly dependent on the physicochemical properties of NPs, especially size, surface charge, surface modification, drug encapsulating capacity, and colloidal stabilization (134). During the design of NPs, it is important

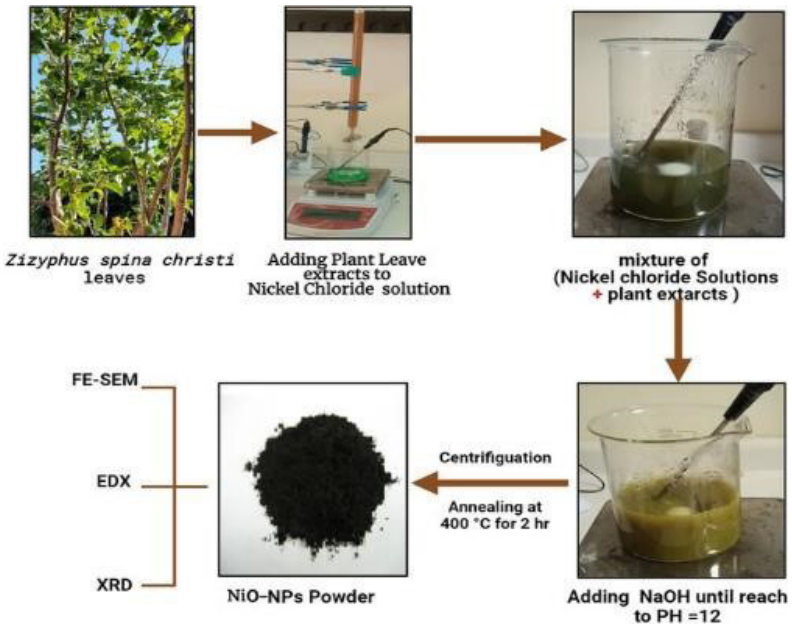

Figure 8. Preparation of NiO NPs derived from *Ziziphus spina-christi* L leaf extract to assay scolicidal activity
Reprinted with permission from Shnawa *et al.* published under a CC BY 4.0 license
FE-SEM: Field emission scanning electron microscopy; EDX: Energy-dispersive X-ray analysis; XRD: X-ray Diffraction; NiO NPs: Nickel oxide nanoparticles

to carefully manage the size and size distribution of nanocarriers, as size affects pharmacokinetics (PK), safety, and biodistribution (52, 134). A sub-200 nm size is ideal for drug delivery and can address some challenges of large-sized NPs, such as bioavailability and *in vivo* instability (52).

The charge and functional groups on the NPs' surface are other factors that play an important role in their uptake, stability, opsonization, and interactions with plasma proteins (59). By proper formulation of NPs, the dissolution rates and, therefore, bioavailability will increase. Biological barriers in the gastrointestinal tract (GIT) limit the oral absorption of hydrophobic drugs (135). Despite advances in NP-based formulations that enhance oral efficacy, the intracellular trafficking of NPs remains poorly understood, and oral bioavailability remains unresolved. Functionalizing NPs surfaces with peptides, antibodies, and aptamers can

Table 5. Selenium, copper, TiO_2, NiO, CeO_2 nanoparticles drug delivery systems for the treatment of hydatid cyst

Type	Components/ Delivery agents	Treatment model	Dosage	Treatment Time	Effect	Ref.
Selenium NPs (SeNPs)	Green biosynthesized SeNPs by Bacillus spp. MSh-1	PSCs	50-500 µg/ml	10-60 min	Strong scolicidal effects for use in CE surgery	(124)
	AgNPs/ SeNPs	PSCs	500, 250, 125, and 50 µg/ml	10-60 min	A protoscolicidal effect	(125)
	SeNPs	Mice	150, 200 µg/ml	5 months	Reduction the number of cysts	(126)
	Green CuNPs synthesized by *C. spinosa* extract alone and combined with ABZ	PSCs	CuNPs: 250, 500, and 750 mg/ml ABZ: 200 mg/ml	5-60 min	A strong scolicidal effects, especially in combination with ABZ The activation of apoptosis	(10)
Copper NPs (CuNPs)	Green-synthesized CuNPs using *L. arcticus* extract	Mice	80 mg/kg	28 days	A remarkable decrease in size, weight, number, oxidative stress markers, and inflammatory cytokines	(127)
	CuO/γ-Al_2O_3/with or without CS, using *R. officinalis* extract	PSCs	1.6 mg/ml CuO	60 min	A highest scolicidal effect	(128)
Titanium oxide NPs (TiO_2 NPs)	sea urchin *E. mathaei* and TiO_2 NPs	Mice	15 µg/ml	3 months	Reduction in the volume, size, and number of cysts	(129)
	TiO_2 NPs	PSCs	250, 500, 1000, 2000, and 4000 µg/ml	15-60 min	Destroying PSCs	(131)
Zirconium Oxide (ZrO_2) NPs	ZrO_2 NPs				Highest fatality rate	(130)
nickel oxide NPs (NiO NPs)	NiO NPs derived from *Z. spina-christi* L leaf extract	PSCs	6.25-100 µg/ml	10-120 min	A potent reducing and capping agent Strong antioxidant activity and low toxicity of NiO-NPs on red blood	(132)
Cerium oxide NPs (CeO_2 NPs)	*H. leucospilota* extract and CeO_2 NPs	Mice	15 and 20 mg/ml	4 weeks	Significant reduction in the number, size, and volume of cysts	*(133)*

SeNPs: Selenium NPs; PSCs: Protoscoleces; CE: Cystic echinococcosis; CuNPs: Copper NPs; ABZ: Albendazole; CuO: Cu oxide; γ-Al_2O_3: Gamma alumina; CS: Chitosan; TiO_2: Titanium oxide; NPs: nanoparticles; ZrO_2: Zirconium oxide; NiO: Nickel oxide; CeO_2: Cerium oxide

enhance their biocompatibility and the delivery of drugs to targeted cells or tissues (70).

The NPs-protein interactions within whole blood and their safety and human toxicity are also the main challenges (52, 59). The biodegradation and dissolution of inorganic NPs (especially metal-based NPs) can affect their subsequent immunological response; it is important to carefully evaluate their biological fate and immune reaction before using them as carriers in drug delivery and other biomedical applications (136). Adjustments to components and parameters during NPs synthesis can achieve an acceptable level of NPs' toxicity and safety (52).

Conclusion and Future Perspectives

Cystic hydatidosis or CE is a chronic parasitic infection with significant mortality that is still considered a neglected disease. The complete surgical removal of CE lesions followed by the oral administration of ABZ, a first-line anti-CE drug, is a commonly recommended treatment. However, as complete excision is often unachievable in most cases, long-term chemotherapy with ABZ remains the primary strategy. Due to ABZ's poor solubility and limited oral bioavailability, full remission is achieved in only a small proportion of patients.

The efficacy of chemotherapeutic treatment for hydatid disease depends on the drug's ability to penetrate the cyst and target both the germinal layer and the PSCs, while maintaining an appropriate drug concentration within the cyst over the treatment duration. To improve this issue, some novel NPs-based carriers have been developed.

Among NPs-based carriers, it was shown that metal NPs exhibit strong scolicidal effects, especially in combination with ABZ, via apoptosis induction. Despite these numerous advantages, to the best of our knowledge, no NPs-based formulations for CE treatment have been commercialized yet, and several challenges remain on the path to clinical translation. Although several studies have reported the protoscolicidal effect of the NPs *in vitro*, it is essential to address some challenges in translating these preclinical findings to clinical applications. A deep understanding of the effective parameters influencing the performance of nanoformulations, standardization of treatment protocols, evaluation of the efficacy of novel therapeutic agents, and the development of tools and models that better reflect clinical conditions may pave the way for successful clinical application. In future investigations, attention should be directed toward the precise release of therapeutic agents from nanocarriers at the site of action. Key aspects include enhancing delivery and uptake performance using targeting units (e.g., aptamers or peptides) and adjusting nanocarrier composition and parameters to achieve desirable, predictable release kinetics.

Acknowledgment

The authors acknowledge the financial support from Guilan University of Medical Sciences, Rasht, Iran (Grant No. IR.GUMS.REC.1402.326).

Authors' Contributions

N Z contributed to the original draft, writing, and critical revision. F A assisted with the original draft, writing, revision, and critical revision. R N was responsible for the study conception and design, as well as writing and critical revision. All authors reviewed and approved the final manuscript.

Conflicts of Interest

All authors declare no financial/commercial conflicts of interest.

Declaration

We have not used any AI tools or technologies to prepare this manuscript.

References

1. Silvestri V, Mushi V, Ngasala B. Hydatidosis. In: Silvestri V, Mushi V, Ngasala B, editors.Vascular Damage in Neglected Tropical Diseases: A Surgical Perspective. Cham: Springer Nature Switzerland; 2024. p. 33–48.
2. Hogea M-O, Ciomaga B-F, Muntean M-M, Muntean A-A, Popa MI, Popa GL. Cystic echinococcosis in the early 2020s: A review. Trop med infect 2024; 9: 36.
3. Calame P, Weck M, Busse-Cote A, Brumpt E, Richou C, Turco C, *et al.* Role of the radiologist in the diagnosis and management of the two forms of hepatic echinococcosis. Insights Imaging 2022; 13: 68.
4. Basinger SC, Khan A, Ahmed H, Afzal MS, Simsek S, Budke CM. Estimation of the monetary burden of treated human cystic echinococcosis in Pakistan. Acta Trop 2021; 222: 106026.
5. Aziz H, Seda P, Awan A, Gosse MD, Krishnakumari AJ, Pawlik TM. Cystic echinococcosis of the liver. J Gastrointest Surg 2025; 29: 101974.
6. Widdicombe J, Basáñez M-G, Entezami M, Jackson D, Larrieu E, Prada JM. The economic evaluation of cystic echinococcosis control strategies focused on zoonotic hosts: A scoping review. PLoS Negl Trop Dis 2022; 16: e0010568.
7. Ghasse AT. Review on epidemiology and public health significance of hydatidosis. Vet Med Int 2020; 2020:8859116.
8. Fakhri Y, Omar SS, Dadar M, Pilevar Z, Sahlabadi F, Torabbeigi M, *et al.* The prevalence of hydatid cyst in raw meat products: A global systematic review, meta-analysis, and meta-regression. Sci Rep 2024; 14: 26094.
9. Sadr S, Lotfalizadeh N, Abbasi AM, Soleymani N, Hajjafari A, Roohbaksh Amooli Moghadam E, *et al.* Challenges and prospective of enhancing hydatid cyst chemotherapy by nanotechnology and the future of nanobiosensors for diagnosis. Trop Med Infect Dis 2023; 8: 494.
10. Ezzatkhah F, Khalaf AK, Mahmoudvand H. Copper nanoparticles: Biosynthesis, characterization, and protoscolicidal effects alone and combined with albendazole against hydatid cyst protoscoleces. Biomed Pharmacother 2021; 136: 111257.
11. Hajjafari A, Sadr S, Santucciu C, Masala G, Bayat M, Lotfalizadeh N, *et al.* Advances in detecting cystic echinococcosis in intermediate hosts and new diagnostic tools: A literature review. Vet Sci 2024; 11: 227.
12. Albalawi AE, Alanazi AD, Baharvand P, Sepahvand M, Mahmoudvand H. High potency of organic and inorganic nanoparticles to treat cystic echinococcosis: An evidence-based review. Nanomaterials 2020; 10: 2538.
13. Darani HY, Ahmadi F, Zabardast N, Yousefi HA, Shirzad H. Development of a latex agglutination test as a simple and rapid method for diagnosis of *Trichomonas vaginalis* infection. Avicenna J Med Biotechnol 2010; 2: 63–66.
14. Kiani H, Haghighi A, Seyyedtabaei SJ, Azargashsb E, Zebardast N, Taghipour N, *et al.* Prevalence, clinical manifestations and genotyping of Cryptosporidium spp. In patients with gastrointestinal illnesses in western Iran. Iran J Parasitol 2017; 12: 169–176.
15. Baykan A, Aydin E, Koc M, Sahin H, Karul A, Baykan M, *et al.* Hydatid disease: Imaging, treatment, and beyond. Clin Radiol 2025; 80: 106748.
16. Tamarozzi F, Silva R, Fittipaldo VA, Buonfrate D, Gottstein B, Siles-Lucas M. Serology for the diagnosis of human hepatic cystic echinococcosis and its relation with cyst staging: A systematic review of the literature with meta-analysis. PLoS Negl Trop Dis

2021; 15: e0009370.
17. Sharma A, Badea M, Tiwari S, Marty JL. Wearable biosensors: An alternative and practical approach in healthcare and disease monitoring. Molecules 2021; 26: 748.
18. Li L, Wang T, Zhong Y, Li R, Deng W, Xiao X, *et al.* A review of nanomaterials for biosensing applications. J Mater Chem B 2024; 12: 1168–1193.
19. Kamali H, Golmohammadzadeh S, Zare H, Nosrati R, Fereidouni M, Safarpour H. The recent advancements in the early detection of cancer biomarkers by DNAzyme-assisted aptasensors. J Nanobiotechnology 2022; 20: 438.
20. Jahani Z, Meshgi B, Rajabi-Bzl M, Jalousian F, Hasheminasab S. Improved serodiagnosis of hydatid cyst disease using gold nanoparticle labeled antigen B in naturally infected sheep. Iran J Parasitol 2014; 9: 218.
21. Khalilpour A, Sadjjadi SM, Moghadam ZK, Yunus MH, Zakaria ND, Osman S, *et al.* Lateral flow test using *Echinococcus granulosus* native antigen B and comparison of IgG and IgG4 dipsticks for detection of human cystic echinococcosis. Am J Trop Med Hyg 2014; 91: 994.
22. Li P, Jia Z, Lü G. Hydatid detection using the near-infrared transmission angular spectra of porous silicon microcavity biosensors. Sci Rep 2017; 7: 1–8.
23. Li Y, Jia Z, Lv G, Wen H, Li P, Zhang H, *et al.* Detection of *Echinococcus granulosus* antigen by a quantum dot/porous silicon optical biosensor. Biomed Opt Express 2017; 8: 3458–3469.
24. Jafari F, Maghsood AH, Fallah M, Jalilvand A, Matini M, Amini B. Design of highly sensitive nano-biosensor for diagnosis of hydatid cyst based on gold nanoparticles. Photodiagnosis Photodyn Ther 2022; 38: 102786.
25. Shirazi S, Hoghooghi-Rad N, Madani R. The comparison between AgB-ELISA and a new method of Nano-ELISA for diagnosis of hydatidosis in sheep. J Hellenic Vet Med Soc 2022; 73: 3629–3634.
26. Khoronko Y, Ermakova L, Pshenichnaya N. Current approaches to diagnostics and treatment of hydatid echinococcosis. Int J Infect Dis 2022; 116: S74.
27. Ebenezer O, Oyetunde-Joshua F, Omotoso OD, Shapi M. Benzimidazole and its derivatives: Recent Advances (2020–2022). Results Chem 2023; 5: 100925.
28. Lee YT, Tan YJ, Oon CE. Benzimidazole and its derivatives as cancer therapeutics: The potential role from traditional to precision medicine. Acta Pharm Sin B 2023; 13: 478–497.
29. Chai J-Y, Jung B-K, Hong S-J. Albendazole and mebendazole as anti-parasitic and anti-cancer agents: An update. Korean J Parasitol 2021; 59: 189.
30. Gong Y, Zhou T, Ma R, Yang J, Zhao Y, Pan M, *et al.* Efficacy and mechanism of energy metabolism dual-regulated nanoparticles (atovaquone-albendazole nanoparticles) against cystic echinococcosis. BMC Infect Dis 2024; 24: 778.
31. Su D, Bai M, Wei C, Long X, Liu X, Shen X, *et al.* Combining solubilization and controlled release strategies to prepare pH-sensitive solid dispersion loaded with albendazole: *In vitro* and *in vivo* studies. Front Vet Sci 2024; 11: 1522856.
32. Koradia KD, Parikh RH, Koradia HD. Albendazole nanocrystals: Optimization, spectroscopic, thermal and anthelmintic studies. J Drug Deliv Sci Technol 2018; 43: 369–378.
33. Zubair T, Rashid SA, Bristy NL, Banik S, Sultana S, Mojumder TJ, *et al.* Nanocarriers as drug delivery system for chemotherapeutic agents: From inception to clinical implementation. Drug Dev Ind Pharm 2025; 51: 1699-1717.
34. Pasut G. Grand challenges in nano-based drug delivery. Front med technol 2019; 1: 1.
35. Rafiei A, Soltani S, Ramezani Z, Abbaspour MR, Jelowdar A, Kahvaz MS. Ultrastructural changes on fertile and infertile hydatid cysts induced by conventional and solid lipid nanoparticles of albendazole and albendazole sulfoxide. Comp Clin Path 2019; 28: 1045–1053.
36. Nsairat H, Khater D, Sayed U, Odeh F, Al Bawab A, Alshaer W. Liposomes: Structure, composition, types, and clinical applications. Heliyon 2022; 8: e09394.
37. Dymek M, Sikora E. Liposomes as biocompatible and smart delivery systems–the current state. Adv Colloid Interface Sci 2022; 309: 102757.
38. Lv H, Jiang Y, Liao M, Sun H, Zhang S, Peng X. *In vitro* and *in vivo* treatments of *Echinococcus granulosus* with Huaier aqueous extract and albendazole liposome. Parasitol Res 2013; 112: 193–198.
39. Li H, Song T, Shao Y, Aili T, Ahan A, Wen H. Comparative evaluation of liposomal albendazole and tablet-albendazole against hepatic cystic echinococcosis: A non-randomized clinical trial. Medicine 2016; 95: e2237.
40. Zhang H, Zhao J, Chen B, Ma Y, Li Z, Shou X, *et al.* Pharmacokinetics and tissue distribution study of liposomal albendazole in naturally *Echinococcus granulosus* infected sheep by a validated UPLC-Q-TOF-MS method. J Chromatogr B 2020; 1141: 122016.
41. Moghadaszadeh M, Khayyati M, Spotin A, Norouzi R, Pagheh AS, Oliveira SMR, *et al.* Scolicidal and apoptotic activities of 5-hydroxy-1, 4-naphthoquinone as a potent agent against *Echinococcus granulosus* protoscoleces. Pharmaceuticals 2021; 14: 623.
42. Li Z, Ding S, Li Y. Study on the immunity protection of 14-3-3-MPLA–liposome vaccine against cystic echinococcosis in mice. Front lab Med 2018; 2: 146–151.
43. Xiong X, Li J, Gao D, Sheng Z, Zheng H, Liu W. Cell-membrane biomimetic indocyanine green liposomes for phototheranostics of Echinococcosis. Biosensors 2022; 12: 311.
44. Sorouri N, Soleymani N, Sadr S, Rahdar A, Ebrahimzadeh E, Borji H. Investigating the therapeutic effects of curcumin nanocapsules in hydatid cyst-infected mice. Exp Parasitol 2024; 267: 108860.
45. Pandey S, Shaikh F, Gupta A, Tripathi P, Yadav JS. A recent update on solid lipid nanoparticles for effective drug delivery. Adv Pharm Bull 2022; 12: 17.
46. Rajpoot K. Solid lipid nanoparticles: A promising nanomaterial in drug delivery. Curr Pharm Des 2019; 25: 3943–3959.
47. Jelowdar A, Rafiei A, Abbaspour MR, Rashidi I, Rahdar M. Efficacy of combined albendazol and praziquntel and their loaded solid lipid nanoparticles components in chemoprophylaxis of experimental hydatidosis. Asian Pac J Trop Biomed 2017; 7: 549–554.
48. Soltani S, Rafiei A, Ramezani Z, Abbaspour MR, Jelowdar A, Kahvaz MS. Evaluation of the hydatid cyst membrane permeability of albendazole and albendazole sulfoxide-loaded solid lipid nanoparticles. Jundishapur J Nat Pharm Prod 2017; 12: 314-319.
49. Aminpour S, Rafiei A, Jelowdar A, Kouchak M. Evaluation of the protoscolicidal effects of albendazole and albendazole loaded solid lipid nanoparticles. Iran J Parasitol 2019; 14: 127.
50. Kohansal K, Rafiei A, Kalantari H, Jelowdar A, Salimi A, Rezaie A, *et al.* Nephrotoxicity of albendazole and albendazole loaded solid lipid nanoparticles in mice with experimental hydatidosis. Adv Pharm Bull 2022; 12: 102.
51. Faizi F, Mahjub R, Torabi N, Motavallihaghi S, Fallah M. Cationized albumin conjugated solid lipid nanoparticles as vectors for delivery of albendazole against cystic echinococcosis. Parasites Vectors 2024; 17: 542.
52. Kamali H, Nosrati R, Malaekeh-Nikouei B. Nanostructures and their associated challenges for drug delivery (Edited By: Prashant Kesharwani and N.K. Jain). Hybrid nanomaterials for drug delivery. Woodhead Publishing Series in Biomaterials 2022. p. 1-26.
53. Jacob S, Rao R, Gorain B, Boddu SH, Nair AB. Solid lipid nanoparticles and nanostructured lipid carriers for anticancer phytochemical delivery: Advances, challenges, and future prospects. Pharmaceutics 2025; 17: 1079.
54. Ahmadpour E, Godrati-Azar Z, Spotin A, Norouzi R, Hamishehkar H, Nami S, *et al.* Nanostructured lipid carriers of ivermectin as a novel drug delivery system in hydatidosis. Parasit Vectors 2019; 12: 1-9.

55. Chen C, Gao Q, Luo Y, Zhang G, Xu X, Li Z, *et al.* The immunotherapy with hMASP-2 DNA nanolipoplexes against echinococcosis in experimentally protoscolex-infected mice. Acta Trop 2020; 210: 105579.
56. Lee M-K. Liposomes for enhanced bioavailability of water-insoluble drugs: *In vivo* evidence and recent approaches. Pharmaceutics 2020; 12: 264.
57. Guillot AJ, Martínez-Navarrete M, Garrigues TM, Melero A. Skin drug delivery using lipid vesicles: A starting guideline for their development. J Control Release 2023; 355: 624–654.
58. Gatto MS, Johnson MP, Najahi-Missaoui W. Targeted liposomal drug delivery: Overview of the current applications and challenges. Life 2024; 14: 672.
59. Sharma D, Sharma N, Pathak M, Agrawala PK, Basu M, Ojha H. Nanotechnology-based drug delivery systems: Challenges and opportunities (Edited by: Alexandru Mihai Grumezescu). Drug Targeting and Stimuli Sensitive Drug Delivery Systems: Elsevier; 2018. p. 39-79.
60. Satchanska G, Davidova S, Petrov PD. Natural and synthetic polymers for biomedical and environmental applications. Polymers 2024; 16: 1159.
61. Eltaib L. Polymeric nanoparticles in targeted drug delivery: Unveiling the impact of polymer characterization and fabrication. Polymers 2025; 17: 833.
62. Farhadi M, Haniloo A, Rostamizadeh K, Faghihzadeh S. Efficiency of flubendazole-loaded mPEG-PCL nanoparticles: A promising formulation against the protoscoleces and cysts of *Echinococcus granulosus*. Acta Trop 2018; 187: 190–200.
63. Soleymani N, Sadr S, Santucciu C, Rahdar A, Masala G, Borji H. Evaluation of the in-vitro effects of albendazole, mebendazole, and praziquantel nanocapsules against protoscolices of hydatid cyst. Pathogens 2024; 13: 790.
64. Soleymani N, Sadr S, Santucciu C, Rahdar A, Masala G, Borji H. Investigating the therapeutic effects of albendazole, mebendazole and praziquantel nanocapsules in hydatid cyst-infected mice. Pathogens 2025; 14: 240.
65. Gültekin Y, Korkmaz Ç, Öztürk N, Filazi A, Deniz A, Vural İ. Development of phytase targeted PLGA nanoparticles loaded with albendazole sulfoxide and praziquantel and evaluation of efficacy on the hydatid cysts. J Drug Deliv Technol 2025; 105: 106662.
66. Aboelsoued D, Toaleb NI, Ibrahim S, Ibrahim S. *In vitro* and *ex vivo* protoscolicidal effect of poly(amidoamine) nanoemulsion against *Echinococcus granulosus*. Sci Rep 2024; 14: 11957.
67. Moheteer A, Zhu J, Pang D, Rao X, Aini A, Aimulajiang K, *et al.* Dihydroartemisinin-sodium taurocholate-PLGA nanoparticles: A novel therapeutic approach against cystic echinococcosis. Front Pharmacol 2025; 16: 1600525.
68. Kazemi Asl S, Rahimzadegan M, Ostadrahimi R. The recent advancement in the chitosan hybrid-based scaffolds for cardiac regeneration after myocardial infarction. Carbohydr Polym 2023; 300: 120266.
69. Román-Doval R, Torres-Arellanes SP, Tenorio-Barajas AY, Gómez-Sánchez A, Valencia-Lazcano AA. Chitosan: Properties and its application in agriculture in context of molecular weight. Polymers 2023; 15: 2867.
70. Mikušová V, Mikuš P. Advances in chitosan-based nanoparticles for drug delivery. Int J Mol Sci 2021; 22: 9652.
71. Liu Y, Wang Xq, Ren Wx, Chen Yl, Yu Y, Zhang Jk, *et al.* Novel albendazole–chitosan nanoparticles for intestinal absorption enhancement and hepatic targeting improvement in rats. J Biomed Mater Res B Appl Biomater 2013; 101: 998–1005.
72. Torabi N, Dobakhti F, Faghihzadeh S, Haniloo A. *In vitro* and *in vivo* effects of chitosan-praziquantel and chitosan-albendazole nanoparticles on *Echinococcus granulosus* Metacestodes. Parasitol Res 2018; 117: 2015–2023.
73. Napooni S, Delavari M, Arbabi M, Barkheh H, Rasti S, Hooshyar H, *et al.* Scolicidal effects of chitosan–curcumin nanoparticles on the hydatid cyst protoscolices. Acta Parasitol 2019; 64: 367–375.
74. Kishik S, Nagati I, El Hayawan I, Ali I, Fawzy M, Ali H. Efficacy of *Nigella sativa* oil and its chitosan loaded nanoparticles on experimental cystic echinoncoccosis with immunological assessment. Parasitol United J 2020; 13: 172–178.
75. Darvishi MM, Moazeni M, Alizadeh M, Abedi M, Tamaddon A-M. Evaluation of the efficacy of albendazole sulfoxide (ABZ-SO)–loaded chitosan-PLGA nanoparticles in the treatment of cystic echinococcosis in laboratory mice. Parasitol Res 2020; 119: 4233–4241.
76. Firouzeh N, Eslaminejad T, Shafiei R, Faridi A, Fasihi Harandi M. Lethal *in vitro* effects of optimized chitosan nanoparticles against protoscoleces of *Echinococcus granulosus*. J Bioact Compat 2021; 36: 237–248.
77. Li Y, Zhu Y, Sha T, Chen Z, Yu M, Zhang F, *et al.* A multi-epitope chitosan nanoparticles vaccine of canine against *Echinococcus granulosus*. J Biomed Nanotechnol 2021; 17: 910–920.
78. Amirafshari H, Khazaal RM, Marzban A, Cheraghipour K, Masoori L, Sepahvand A, *et al.* Therapeutic effects of zinc oxide nanoparticles encapsulated within chitosan-camphor against hydatid cysts through suppressing oxidative stress, inflammation, and DNA damage. Biomed Pharmacother 2025; 188: 118128.
79. Abd El-Latif NF, Elsayad M, Abdulsalam DE, El-Hadidy W, Khodear GAM, Kazem A, *et al.* Evaluation of the therapeutic efficacy of albendazole and nitazoxanide loaded chitosan nanoparticles against experimental echinococcosis. J Parasit Dis 2025; 49: 1055-1067.
80. Bhardwaj H, Jangde RK. Current updated review on preparation of polymeric nanoparticles for drug delivery and biomedical applications. Next Nanotechnol 2023; 2: 100013.
81. Nelemans LC, Gurevich L. Drug delivery with polymeric nanocarriers-cellular uptake mechanisms. Materials 2020; 13: 366.
82. Han J, Zhao D, Li D, Wang X, Jin Z, Zhao K. Polymer-based nanomaterials and applications for vaccines and drugs. Polymers 2018; 10: 31.
83. Sánchez L-F, Cánepa J, Kim S, Nakamatsu J. A simple approach to produce tailor-made chitosans with specific degrees of acetylation and molecular weights. Polymers 2021; 13: 2415.
84. Alemu D, Getachew E, Mondal AK. Study on the physicochemical properties of chitosan and their applications in the biomedical sector. Int J Polym Sci 2023; 2023: 5025341.
85. Madni A, Kousar R, Naeem N, Wahid F. Recent advancements in applications of chitosan-based biomaterials for skin tissue engineering. J Bioresour Bioprod 2021; 6: 11–25.
86. Ji M, Long L, Xiong S, Liu Z, Luo J, Liu D. Nanocrystalline drug delivery systems for natural compounds: Progress, challenges and future opportunities. Int J Nanomedicine 2025; 20: 11315–11339.
87. Sood R, Tomar D, Kaushik P, Sharma P, Rani N, Guarve K, *et al.* Enhanced solubility and increased bioavailability with engineered nanocrystals. Curr Drug Ther 2024; 19: 638–647.
88. Parveen N, Abourehab MAS, Thanikachalam PV, Khar RK, Kesharwani P. Nanocrystals as an emerging nanocarrier for the management of dermatological diseases. Colloids Surf B Biointerfaces 2023; 225: 113231.
89. Paredes AJ, Bruni SS, Allemandi D, Lanusse C, Palma SD. Albendazole nanocrystals with improved pharmacokinetic performance in mice. Ther Deliv 2018; 9: 89–97.
90. Paredes AJ, Camacho NM, Schofs L, Dib A, Zarazaga MdP, Litterio N, *et al.* Ricobendazole nanocrystals obtained by media milling and spray drying: Pharmacokinetic comparison with the micronized form of the drug. Int J Pharm 2020; 585: 119501.
91. Permana AD, Paredes AJ, Zanutto FV, Amir MN, Ismail I, Bahar MA, *et al.* Albendazole nanocrystal-based dissolving microneedles with improved pharmacokinetic performance for enhanced treatment of cystic echinococcosis. ACS Appl Mater Interfaces 2021; 13: 38745–38760.
92. Liang Z, Chen M, Yan Y, Chen D, Xie S. Nanocrystal suspensions for enhancing the oral absorption of albendazole. Nanomaterials 2022; 12: 3032.
93. Hu C, Liu Z, Liu C, Zhang Y, Fan H, Qian F. Improvement of antialveolar echinococcosis efficacy of albendazole by a novel nanocrystalline formulation with enhanced oral bioavailability. ACS Infect Dis 2019; 6: 802–810.

94. Fateh R, Norouzi R, Mirzaei E, Nissapatron V, Nawaz M, Khalifeh-Gholi M, *et al. In vitro* evaluation of albendazole nanocrystals against *Echinococcus granulosus* protoscolices. Ann Parasitol 2021; 67: 203–212.
95. Montiel Schneider MG, Martín MJ, Otarola J, Vakarelska E, Simeonov V, Lassalle V, *et al.* Biomedical applications of iron oxide nanoparticles: Current insights progress and perspectives. Pharmaceutics 2022; 14: 204.
96. Abidi H, Ghaedi M, Rafiei A, Jelowdar A, Salimi A, Asfaram A, *et al.* Magnetic solid lipid nanoparticles co-loaded with albendazole as an anti-parasitic drug: Sonochemical preparation, characterization, and *in vitro* drug release. J Mol Liq 2018; 268: 11–18.
97. Li Z, Zhang G, Luo Y, Gao Q, Wang J, Chen C, *et al. In vivo* effect of magnetic microspheres loaded with E2-a in the treatment of alveolar echinococcosis. Sci Rep 2020; 10: 1–8.
98. Kumar P, Chandra P, Verma N, Diksha, Sharma A, Mani M, *et al.* Gold nanoparticles: An emerging novel technology for targeted delivery system for site-specific diseases. Curr Drug Ther 2025; 20: 345–361.
99. Çolak B, Aksoy F, Yavuz S, Demircili ME. Investigating the effect of gold nanoparticles on hydatid cyst protoscolices under low-power green laser irradiation. Turk J Surg 2019; 35: 314.
100. Barabadi H, Honary S, Ali Mohammadi M, Ahmadpour E, Rahimi MT, Alizadeh A, *et al.* Green chemical synthesis of gold nanoparticles by using *Penicillium aculeatum* and their scolicidal activity against hydatid cyst protoscolices of *Echinococcus granulosus*. Environ Sci Pollut Res Int 2017; 24: 5800–5810.
101. Malekifard F. Solicidal effect of the gold nanoparticle on protoscoleces of hydratid cyst *in vitro*. Stud Med Sci 2017; 28: 130–137.
102. Napooni S, Arbabi M, Delavari M, Hooshyar H, Rasti S. Lethal effects of gold nanoparticles on protoscolices of hydatid cyst: *in vitro* study. Comp Clin Path 2019; 28: 143–150.
103. Zarei Z, Azarnivand H, Moazeni M, Bahmani M, Razmjoue D, Oroojalian F. *Salvia sclarea* L. mediated green synthesis of gold nanoparticles (AuNPs) and evaluation of their antibacterial, anticandidal, and scolicidal properties. Sci Rep 2025; 15: 33392.
104. Zhou X-Q, Hayat Z, Zhang D-D, Li M-Y, Hu S, Wu *et al.* Zinc oxide nanoparticles: synthesis, characterization, modification, and applications in food and agriculture. Processes 2023; 11: 193.
105. Deka B, Baruah C, Babu A, Kalita P. Biological and non-conventional synthesis of zinc oxide nanoparticles (ZnO-NPs): their potential applications. J Nanotechnol Nanomater 2022; 3: 79–89.
106. Norouzi R, Hejazy M, Ataei A. Scolicidal activity of zinc oxide nanoparticles against hydatid cyst protoscolices *in vitro*. Nanomed Res J 2019; 4: 23–28.
107. Mahmmoud SM, Albayati NY, Abdullah AH. Effect of ZnO nanoparticles on protoscolices of *Echinococcus granulosus* and comparing them with aqueous extract of the grape seeds. Biochem Cell Arch 2020; 20: 2209–2213.
108. Shakibaie M, Khalaf AK, Rashidipour M, Mahmoudvand H. Effects of green synthesized zinc nanoparticles alone and along with albendazole against hydatid cyst protoscoleces. Ann med surg 2022; 78: 103746.
109. Shnawa BH, Hamad SM, Barzinjy AA, Kareem PA, Ahmed MH. Scolicidal activity of biosynthesized zinc oxide nanoparticles by *Mentha longifolia* L. leaves against *Echinococcus granulosus* protoscolices. Emergent Mater 2022; 5: 683–693.
110. Cheraghipour K, Azarhazine M, Zivdari M, Beiranvand M, Shakib P, Rashidipour M, *et al.* Evaluation of scolicidal potential of salicylate coated zinc nanoparticles against *Echinococcus granulosus* protoscoleces. Exp Parasitol 2023; 246: 108456.
111. Bagherivand A, Jafarirad S, Norouzi R, Rezazadeh E, Karimi A. Zinc oxide/barite nanocomposite from *Trachyspermum ammi* plant extract: A novel agent against protoscolices of *Echinococcus granulosus*. J Drug Deliv Technol 2024; 100: 106024.
112. Albalawi Aishah E, Shater Abdullah F, Alanazi Abdullah D, Alsulami Muslimah N, Almohammed Hamdan I. High potency of linalool-zinc oxide nanocomposite as a new agent for cystic echinococcosis treatment. Antimicrob Agents Chemother 2024; 68: e01734–01723.
113. Lashkarizadeh MR, Asgaripour K, Dezaki ES, Harandi MF. Comparison of scolicidal effects of amphotricin B, silver nanoparticles, and *Foeniculum vulgare* Mill on hydatid cysts protoscoleces. Iran J Parasitol 2015; 10: 206.
114. Rahimi MT, Ahmadpour E, Esboei BR, Spotin A, Koshki MHK, Alizadeh A, *et al.* Scolicidal activity of biosynthesized silver nanoparticles against *Echinococcus granulosus* protoscolices. Int J Surg 2015; 19: 128–133.
115. Jalil PJ, Shnawa BH, Hamad SM. Silver nanoparticles: Green synthesis, characterization, blood compatibility and protoscolicidal efficacy against *Echinococcus granulosus*. Pak Vet J 2021; 41: 393–399.
116. Hamad SM, Shnawa BH, Jalil PJ, Ahmed MH. Assessment of the therapeutic efficacy of silver nanoparticles against secondary cystic echinococcosis in BALB/c mice. Surfaces 2022; 5: 91–112.
117. Nassef NE, Saad A-GE, Harba NM, Beshay EVN, Gouda MA, Shendi SS, *et al.* Evaluation of the therapeutic efficacy of albendazole-loaded silver nanoparticles against *Echinococcus granulosus* infection in experimental mice. J Parasit Dis 2019; 43: 658–671.
118. Jari SD, Yousif JJ. Therapeutic effects of silver nanoparticles loaded with albendazole, albendazole drugs in male albino mice infected with hydatid cysts. Int J Adv Sci Res 2020; 1: 13–18.
119. Aljanabi AA, Al-Mosawi KAM, Bashi AM. Scolicidal effects of silver–copper (core-shell) nanoparticles against *Echinococcus granulosus* protoscolices *in vitro*. Ann Rom Soc Cell Biol 2021; 25: 4335–4342.
120. Baghdadi HBA. Potential use of silver nanoparticles green synthesized using *Astragalus spinosus* extract for treating cystic echinococcosis. Acta Tropica 2024; 257: 107296.
121. Navvabi R, Razmjoue D, Bahmani M, Lysiuk R, Oroojalian F. Eco-friendly green synthesis of silver nanoparticles using *Daphne mucronata* royle seeds extract and the potential antibacterial, antifungal, and scolicidal activities. ChemistrySelect 2024; 9: e202403423.
122. Zarei Z, Razmjoue D, Moazeni M, Azarnivand H, Oroojalian F. *Salvia sclarea* L. (Clary Sage) flower extract-mediated green synthesis of silver nanoparticles and their characterization, antibacterial, antifungal, and scolicidal activities against *Echinococcus granulosus*. Microbe 2024; 5: 100216.
123. Bagherivand A, Jafarirad S, Norouzi R, Karimi A. Scolicidal and apoptotic effects of phyto- and chemically synthesized silver/boehmite nanocomposites on *Echinococcus granulosus* protoscoleces. Biomater Adv 2024; 157: 213723.
124. Mahmoudvand H, Harandi MF, Shakibaie M, Aflatoonian MR, ZiaAli N, Makki MS, *et al.* Scolicidal effects of biogenic selenium nanoparticles against protoscolices of hydatid cysts. Int J Surg 2014; 12: 399-403.
125. Nematollahi A, Shahbazi P, Rafat A, Ghanbarlu M. Comparative survey on scolicidal effects of selenium and silver nanoparticles on protoscolices of hydatid cyst. Open Vet J 2018; 8: 374–377.
126. Mohammed SA, Ali AA. Effect of selenium nanoparticles against protoscoleces of *Echinococcus granulosus in vitro* and hydatid cysts in mice. Iraqi J Vet Sci 2022; 36: 195-202.
127. Alshehri ZS, Alanazi AD, Baghdadi HBA. Therapeutic effects of green synthesized copper nanoparticles against hydatid disease through inhibiting inflammation, oxidative stress, and apoptosis. Acta Parasitol 2025; 70: 73.
128. Bagherivand A, Jafarirad S, Norouzi R, Karimi A. Biomedical behaviors of CuO/γ-alumina/chitosan nanocomposites: Scolicidal and apoptotic effects on hydatid cysts protoscolices. Int J Biol Macromol 2024; 263: 130515.
129. Navvabi A, Homaei A, Khademvatan S, Ansari MHK, Keshavarz M. Combination of TiO_2 nanoparticles and *Echinometra mathaeis* gonad extracts: *In vitro* and *in vivo* scolicidal activity against hydatid cysts. Biocatal Agric Biotechnol 2019; 22: 101432.

130. Ibrahim AA-J. Scolicidal activity of zirconium oxide (ZrO_2) nanoparticles against protoscolices of hydatid cysts. Indian J Forensic Med Toxicol 2020; 14: 409.
131. Ibrahim AAJ. Study the efficacy of titanium oxide (TiO_2) nanoparticles against protoscolices of hydatid cysts. Ann Trop Med Public Health 2020; 23: 60-64.
132. Shnawa BH, Jalil PJ, Hamad SM, Ahmed MH. Antioxidant, protoscolicidal, hemocompatibility, and antibacterial activity of nickel oxide nanoparticles synthesized by *Ziziphus spina-christi*. Bionanoscience 2022; 12: 1264–1278.
133. Aryamand S, Khademvatan S, Tappeh KH, Heshmatian B, Jelodar A. In vitro and in vivo scolicidal activities of *Holothuria leucospilota* extract and CeO_2 nanoparticles against hydatid cyst. Iran J Parasitol 2019; 14: 269.
134. Khizar S, Alrushaid N, Khan FA, Zine N, Jaffrezic-Renault N, Errachid A, *et al.* Nanocarriers based novel and effective drug delivery system. Int J Pharm 2023; 632: 122570.
135. Liu S, Wen X, Zhang X, Mao S. Oral delivery of biomacromolecules by overcoming biological barriers in the gastrointestinal tract: An update. Expert Opin Drug Deliv 2023; 20: 1333–1347.
136. Spirescu VA, Chircov C, Grumezescu AM, Vasile BŞ, Andronescu E. Inorganic nanoparticles and composite films for antimicrobial therapies. Int J Mol Sci 2021; 22: 4595.