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TREATMENT AND PROPHYLAXIS - REVIEW

Therapeutic efficacy of nanocompounds in the treatment of cystic and alveolar echinococcoses: challenges and future prospects

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Abstract

Echinococcus granulosus sensu lato and *E. multilocularis* are the causative agents of life-threatening cystic and alveolar echinococcoses (CE and AE), respectively, which lead to serious public health concerns across the globe. Benzimidazoles (BMZs) are the drugs of choice for the treatment of human CE and AE. Presently, the chemotherapeutic failures of BMZs against CE and AE are caused by their low aqueous solubility, poor absorption, and consequently their erratic bioavailability. Among the BMZ compounds used for CE/AE treatment, albendazole (ABZ) and mebendazole (MBZ) are the only drugs licensed for human use. Nevertheless, the administration of these BMZs for a long period of time leads to undesirable adverse effects. Therefore, there is an urgent need for designing new formulations of BMZs with increased bioavailability. To bridge these therapeutic gaps, nanoparticle enantiomers of ABZ and drug delivery systems based on nanostructured entities currently provide an interesting new formulation of already existing drugs to improve the pharmacokinetic effects of BMZs. This study provides an overview of the tested nanocompounds against *E. granulosus* and *E. multilocularis*, including their effective dose, type of nanoparticles (NPs), assay setting, and therapeutic outcomes. This review suggests that BMZ derivatives loaded in NPs can significantly improve the scolicidal and cysticidal activities compared with single BMZ. Moreover, BMZ-loaded polymeric NPs show a tendency to increase mortality rate against protoscoleces and microcysts compared with metallic formulations, nanoemulsions, lipid nanocapsules, solid lipid NPs, liposomes, and nanocrystals. In the future, the use of the newly structured entities, attained by bridging ligands to the modified surface of NPs, as well as the electromagnetically produced nanodrugs could be helpful for developing fine-tuned formulations as an alternative to the already existing drugs against these neglected parasitic infections.

Keywords Nanocompounds · Scolicidal agents · Cystic echinococcosis · Alveolar echinococcosis · Benzimidazoles

Abbreviations

BMZs	Benzimidazoles
ABZ	Albendazole
MBZ	Mebendazole
NPs	Nanoparticles
NEs	Nanoemulsions
NCs	Nanocrystals
MNPs	Metallic NPs
PZQ	Praziquantel
SeNPs	Selenium NPs

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AgNPs	Silver NPs
ZnONPs	Zinc oxide NPs
SLNs	Solid lipid NPs
ABZSO	Albendazole sulfoxide
L-ABZ	Liposomized albendazole
mPEG-PCL	Methoxy polyethylene glycol-polycaprolactone
PLGA-PEG	Polylactic-co-glycolic acid
PLA	Polylactide
ChABZ	Chitosan-albendazole
ChPZQ	Chitosan-praziquantel

Introduction

Cystic and alveolar echinococcoses (CE/AE) are cyclozoonotic helminthic infections caused by the larval stages of *Echinococcus granulosus* sensu lato (s.l.) and *E. multilocularis*, respectively. More than one million people are estimated to be infected at a global level (Higuita et al. 2016). Canids are the definitive hosts for the adult stage of both parasites. Since livestock and rodents act as the main intermediate hosts for *E. granulosus* and *E. multilocularis*, respectively, they can be infected by the larval stage after the ingestion of infective eggs (Mahami Oskouei et al. 2016; Rostami et al. 2015). Humans act as dead-end hosts for the larval stages (Eckert and Deplazes 2004; Ghabouli-Mehrabani et al. 2014; Siles-Lucas and Hemphill 2002). According to the WHO Informal Working Group on Echinococcosis (WHO-IWGE), the current consensus for the management of CE is based on imaging with a stage-specific approach, resulting in four options for the clinical management: surgery, percutaneous interventions, drug treatment with benzimidazole (BMZ), and "watch and wait" (Brunetti et al. 2010). Albendazole (ABZ) is usually the first therapeutic option, and mebendazole (MBZ) is only applied when ABZ is not well tolerated by patients (Siles-Lucas et al. 2018). Early diagnosis and radical surgery followed by anti-infective prophylaxis with ABZ or MBZ remains one of the few options in AE patients (Brunetti et al. 2010; Hajizadeh et al. 2013).

The pharmaceutical criteria for improved treatment of human AE and CE should be lower adverse effects, higher solubility, and the absence of erratic bioavailability of drugs. Currently, chemotherapeutic drugs against CE/AE are limited to BMZ derivatives (Kohansal et al. 2017). ABZ acts parasitostatically, rather than parasiticidally. Furthermore, the prescribed dosage of ABZ (15 mg/kg/day) for CE treatment has occasionally led to some adverse effects in patients (5 to 40% of cases) such as liver toxicity, severe leukopenia, thrombocytopenia, alopecia, teratogenic reactions, and even embryotoxicity (Hemphill et al. 2014). The chemotherapeutic failure in the treatment of human CE/AE is mainly due to the poor absorption of BMZ drugs by gastrointestinal wall layers, which reduces the drug levels in plasma and in hydatid cyst fluid (Lötsch et al. 2016). Taking together, it seems that design, modification, and delivery of BMZs with lower adverse effects, higher solubility, increased absorption, and long-term efficacy are crucial for the effective treatment of CE and AE. To compensate these therapeutic pitfalls, nanomedicine may represent an innovative approach for the treatment of these neglected parasitic infections. Nanotechnology provides intriguing nanostructured entities since they can control the release of drugs over the time and increase drug targeting capabilities (Forrest and Kwon 2008). In the last years, new approaches to improve the therapeutic effects of nanoparticles (NPs) with BMZs against AE/CE have been tested and some have shown promising scolicidal and cysticidal effects both in vitro and in vivo, respectively (Schipper et al. 1997; Shuhua et al. 2002; Silva et al. 2004; Smego Jr and Sebanego 2005; Stojkovic et al. 2009). NPs are minute materials, ranging between 1 and 100 nm in size. This review presents an update on the latest developments in nanocompounds performed against *E. granulosus* and *E. multilocularis*, including effective dose, type of NPs and their challenges, assay settings (in vitro and/or in vivo), and therapeutic outcomes.

Materials and methods

In order to select the papers reporting nanocompounds and their therapeutic efficacy for the treatment of CE and AE, 40 papers were addressed based on six bibliographic databases including Science Direct, Medline, Scopus, PubMed, Google Scholar, and ProQuest between 1993 and May 2019. Finally, 27 articles met our eligibility criteria (various types of NPs and nanodrugs tested against CE and AE in vitro and in vivo conditions) and were thus included in the current study (Fig. 1). The protoscolicidal effects of nanodrugs and their compounds against CE and AE based on the peer-reviewed papers are summarized in Tables 1 and 2.

Current nanodrugs used against human CE and AE

Nanotechnology-based drug delivery systems against CE and AE (nanoemulsions [NEs], liposomes, nanocrystals [NCs], and NPs) were included in the current review. NEs manifest fine oil dispersions in water known as a promising delivery system for diverse kinds of drugs, including biopharmaceuticals (Sharma et al. 2010) (Fig. 2). Liposomes are small spherically shaped vesicles composed from cholesterol or natural nontoxic phospholipids (Akbarzadeh et al. 2013). They can be used in a wide range of pharmaceutical applications (Akbarzadeh et al. 2013). NCs are nanosized materials with a crystalline structure used to compose a 100%

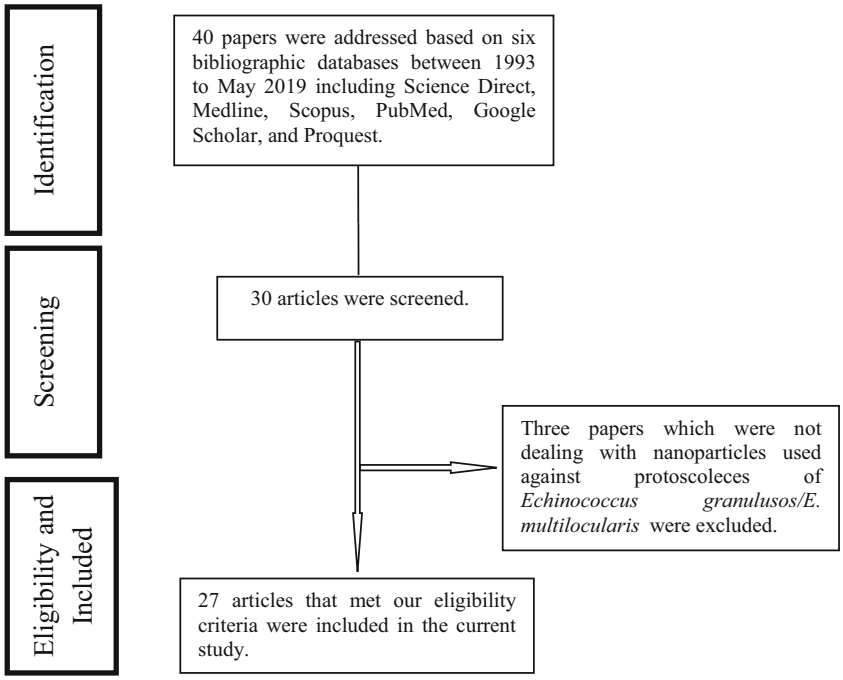

Fig. 1 Flowchart describing the study design process

specific drug, and are suitable for drugs with low solubility (Junghanns and Müller 2008). Different types of NPs with nanomedicine applications are composed of various materials including metals, lipids, and polymers (Gutiérrez et al. 2016). Depending on the process of NP formation, the two main types are nanocapsules or nanospheres. Nanocapsules are vesicular structures made from a nontoxic polymer in which the active compound is placed into a cavity covered by a membrane of the material, while nanospheres are carrier systems in which the active substance is dispersed in the matrix (Prabhu et al. 2015). In addition, NPs can be chemically or biologically synthesized (Hasan 2015).

Metallic NPs

Metallic NPs (MNPs) contain various types of materials, including metal oxide NPs, magnetic NPs, and quantum dots. One of the unique characteristics of MNPs is the variation in the optical properties due to the changes in particle size, which results in displaying different colors at visible wavelengths. The main chemical and physical limitations for the synthesis of MNPs are associated with the use of toxic and hazardous substances and their costs (Mody et al. 2010; Singla et al. 2016). Mahmoudvand et al. (2014) indicated strong scolicidal effects of selenium NPs (SeNPs) biosynthesized by *Bacillus* sp. on protoscoleces (PSCs) of CE in vitro. The SeNPs at 250 and 500 μg/mL concentrations killed all the PSCs after 10 and 20 min of exposure, respectively.

Rahimi et al. (2015) showed the significant scolicidal activity of silver NPs (AgNPs) derived from the aquatic extract of *Penicillium aculeatum* in vitro. In fact, *P. aculeatum* at 0.1 and 0.15 mg/mL concentrations killed 83% and 90% of PSCs after 120 min of exposure, respectively. In contrast, the AgNPs had a poor scolicidal activity against hydatid cyst PSCs, compared with that of amphotericin B and *Foeniculum vulgare* Mill oil. Barabadi et al. (2017) demonstrated considerable scolicidal effects of gold NPs (AuNPs) against hydatid cyst PSCs. The highest PSC mortality (94%) was obtained at a concentration of 0.3 mg/mL after 120 min of exposure in vitro. Moreover, another in vitro study showed significant protoscolicidal effects of AuNPs with 100% mortality of PSCs at the concentration of 1 mg/mL after 60 min of exposure (Malekifard 2017). Napooni et al. (2018) indicated that 76% of the PSCs were destroyed following the exposure to 4 mg/mL of AuNPs after 60 min. Another in vivo study on the secondary infection with CE (intraperitoneal injection of PSCs in mice) compared the therapeutic effects of *Echinacea purpurea*, *Sambucus ebulus*, and zinc oxide NPs (ZnONPs) with those of ABZ showing that the number, size, and masses of cysts in all the treated groups significantly decreased (Razi et al. 2015) (Table 1).

Nanoemulsions

NEs are biphasic systems in which one phase is dispersed in the other. The size of the NE droplets ranges from 10 to 600 nm. There are three types of NEs used to transfer oil-soluble materials, including bicontinuous, water in oil, and oil in water NEs. NEs increase the therapeutic efficacy and reduce side effects and toxic reactions of the drugs. The limitations of NEs are their low stability and low access to

Table 1 Characteristics of nanodrugs and their compounds in treatment of cystic echinococcosis based on the published papers from 2008 to May 2019

Type of nanoparticles	Compound	Disease	Assay setting	Effective dose/duration		Treatment outcome		Reference
				Effective dose	Effective duration	Tested against	Mortality rate (%)	
Metallic (MNPs)	Selenium (SeNPs)	CE	In vitro	*Bacillus* sp. MSh-1 500 mg/mL 10 min		PSCs	100%	Mahmoudvand et al. (2014)
	Silver (AgNPs)	CE	In vitro	*Penicillium aculeatum* 0.15 mg/mL 2 h		PSCs	90%	Rahimi et al. (2015)
		CE	In vitro	4 mg/mL 1 h		PSCs	71.6%	Lashkarizadeh et al. (2015)
	Gold (AuNPs)	CE	In vitro	*P. aculeatum* 0.3 mg/mL 2 h		PSCs	94%	Barabadi et al. (2017)
		CE	In vitro	1 mg/mL 1 h		PSCs	100%	Malekifard (2017)
		CE	In vitro	4 mg/mL 1 h		PSCs	76%	Napooni et al. (2018)
	Zinc oxide (ZnONPs)	CE	In vivo (mice)/IP	5 mg/kg 30 days Daily for 1 month		Cysts	Reduction in the cyst size compared with control	Razi et al. (2015)
Nanoemulsions (NE)		CE	In vitro/in vivo (mice)/IP	NE of a *Zataria multiflora* essential oil In vitro 2 mg/mL 10 min In vivo 20 mg/kg 2 months, daily for 2 months		PSCs Cysts	In vitro 100% In vivo: reduction in the number and cyst size compared with control	Moazeni et al. (2017)
Solid lipid nanoparticles (SLNs)		CE	In vivo (mice)/IP	ABZSO-loaded SLNs 0.5 mg/kg Daily for 15 days		Cysts	Cysts showed reduced size and weight	Ahmadnia et al. (2013)
		CE	In vitro	ABZ- and ABZSO-loaded SLNs 2000 μg/L 72 h		Cysts	Increased permeability of ABZSO over ABZ	(Soltani et al. (2017)
		CE	In vivo (mice)/IP	ABZ- and PZQ-loaded SLNs Dose; ND Daily for 3 months		Cysts	Reduced the weight and size; ABZ-loaded SLNs 83% PZQ-loaded SLNs 85%	Jelowdar et al. (2017)
		CE	In vitro	ABZ- and ABZ-loaded SLNs 250 and 500 μg/mL Days 3 and 7		PSCs Cysts	In vitro 100% Day 5 for nano-ABZ Day 7 for ABZ In vivo: only two mice from the ABZ-loaded SLNs group did not have any cyst	Aminpour et al. (2019)
Liposome		CE	In vitro/in vivo (OA)	In vitro 10 μg/mL L-ABZ + 2 μg/mL *Huaier* aqueous extract		PSCs Cysts		Lv et al. (2013)

Table 1 (continued)

Type of nanoparticles	Compound	Disease	Assay setting	Effective dose/duration		Treatment outcome		Reference
				Effective dose	Effective duration	Tested against	Mortality rate (%)	
					12 days In vivo 75 mg/kg L-ABZ + 15 g/kg *H.* aqueous extract Three times a week for a period of 4 months by the oral route		*Huaier* aqueous extract and L-ABZ are effective against *E. granulosus*	
Lipid nanocapsules (LNCs)		CE	In vivo (mice) OA/SA	ABZ-loaded LNCs 5 mg/kg Daily for 30 days		Cysts	OA 91% efficacy; SA 88% efficacy	Pensel et al. (2015)
Polymeric NPs	PLA	CE	Ex vivo	ABZSO-loaded PLA ND		Cysts	ND	Cong et al. (2008)
	Polyisohexylcyanoacrylate-bound acrylate-bound doxorubicin and PLA	CE	In vitro	ND		PSCs	ND	De et al. (2012)
	Chitosan	CE	In vitro	*Penicillium waksmanii* and *Penicillium citrinum* 200–400 μg/mL 3 h		PSCs	100%	Fakhar et al. (2015)
		CE	In vitro	*Penicillium* extracted Chitosan 200–400 μg/mL 3 h		PSCs	100%	Rahimi-Esboei et al. (2013)
		CE	In vitro/in vivo (IP)	ABZ-loaded chitosan and praziquantel-loaded chitosan In vitro 5 and 10 μg/mL 10 days In vivo 25 mg/kg Daily for 21 days		PSCs Cyst	In vitro 100% mortality on PSC In vivo: no alive microcysts were observed with ChABZ + ChPZQ combination	Torabi et al. (2018)
	ABZSO-loaded PLGA-PEG	CE	In vitro	200 μg/mL 5 min		PSCs	100%	Naseri et al. (2016)
	Flubendazole-loaded mPEG-PCL	CE	In vitro/in vivo (IP)	10 μg/mL Daily for 7 days		PSCs Cyst	In vitro 100% mortality on PSC In vivo: reduction in the weight and number of the cysts (94.64% and 70.21%)	Farhadi et al. (2018)

PSCs, protoscoleces; *ND*, not determined; *OA*, oral administration; *IP*, intraperitoneal; *SA*, subcutaneous administration; *NPs*, nanoparticles; *CE*, cystic echinococcosis; *ABZSO*, albendazole sulfoxide; *PZQ*, praziquantel; *mPEG-PCL*, methoxy polyethylene glycol-polycaprolactone; *PLGA-PEG*, polylactic-co-glycolic acid; *PLA*, polylactide; *ChABZ*, chitosan-albendazole; *ChPZQ*, chitosan-praziquantel; *L-ABZ*, liposomized albendazole

Table 2 Characteristics of nanodrugs and their compounds in treatment of alveolar echinococcosis based on the published papers from 1993 to May 2019

Type of nanoparticles	Compound	Disease	Assay setting/type of administration	Effective dose/duration		Treatment outcome		Reference
				Effective dose	Effective duration	Tested against	Mortality rate (%)	
Liposome		AE	In vivo (mice)/OA	LABZ 35 mg/kg 8 weeks		Cysts	Biomass of cysts is significantly reduced (75–94%)	Wen et al. (1996)
		AE	In vivo (mice)/IP	LABZ 10 mg/kg 4 weeks		Cysts	Parasitostatic effects of ABZ can be enhanced after combining with liposomes	Dvorožňáková et al. (2004)
		AE	In vivo (patients)/OA	LABZ 10 mg/kg 6 months to 10 years		Cysts	LABZ had satisfactory outcome than tablet ABZ	Li et al. (2013)
Nanocrystals (NCs)		AE	In vivo (mice)/IP	ABZ-NCs 5 mg/kg 30 days		Cysts	Weight of the cysts reduced by 77% and the viability of their PSC to 34%	Pensel et al. (2018)
Polymeric NPs	Doxorubicin bound to polyisohexylcyanoacrylate NPs	AE	In vivo (mice)/IP	5 mg/kg 70 and 80 days		Cysts	Doxorubicin bound to polyisohexylcyanoacrylate NPs had an effective anti-parasitic activity	Liance et al. (1993)
	ABZ-loaded PLA	AE	In vivo (mice)/IV	6 mg/kg 30 days		Cysts	ABZ-loaded PLA did not harbor hepatic parasites	Rodrigues Jr et al. (1995)

NPs, nanoparticles; *OA*, oral administration; *IP*, intraperitoneal; *IV*, intravenous; *AE*, alveolar echinococcosis; *LABZ*, liposomized albendazole; *PLA*, polylactide; *NCs*, nanocrystals

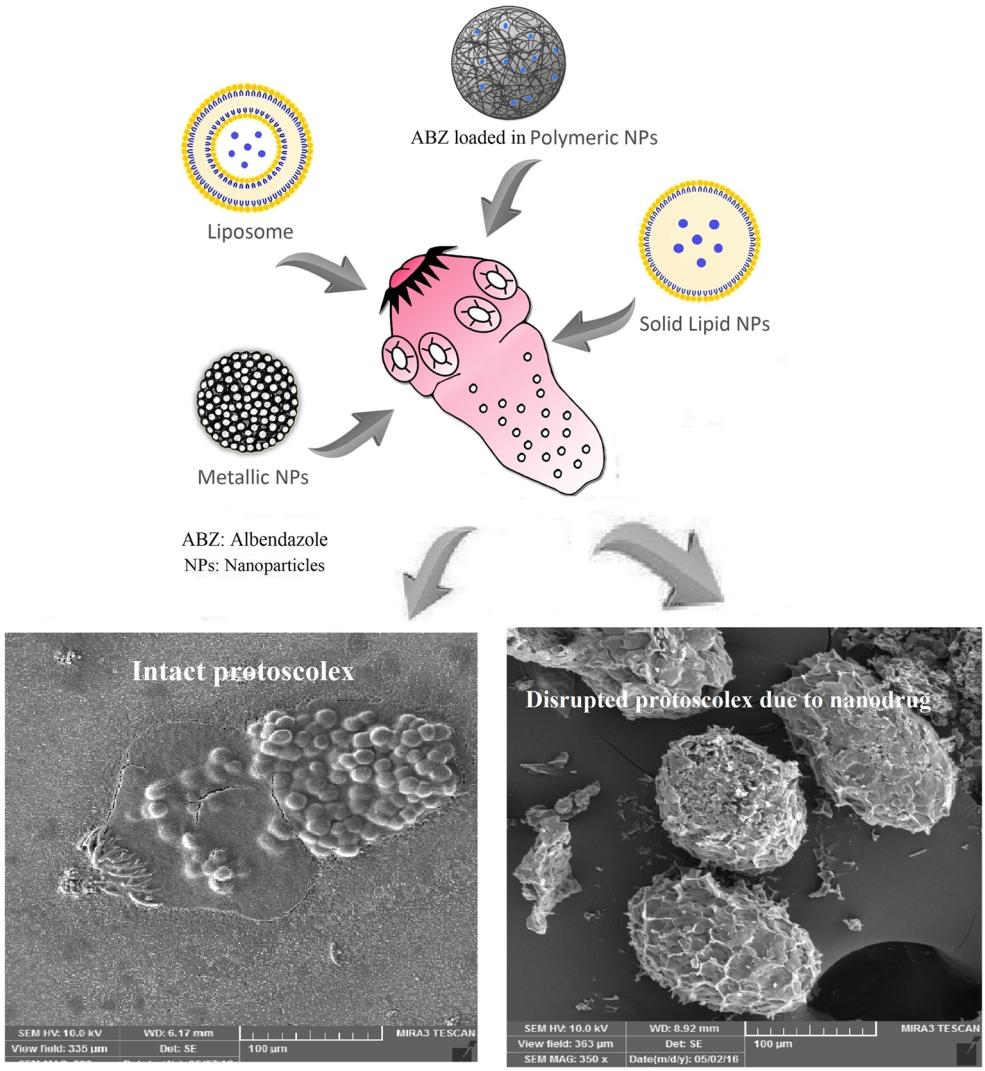

Fig. 2 Scheme of the protoscolicidal properties of various nanomaterials including solid lipid nanoparticles (NPs), metallic NPs, liposome, polymeric NPs, and albendazole loaded in NPs as proposed in this study

surfactants (Jaiswal et al. 2015; Sharma et al. 2010). An in vitro study showed that the scolicidal activity of a *Zataria multiflora* NE against *E. granulosus* PSCs at 2 mg/mL concentration was 100% after 10 min of exposure (Moazeni et al. 2017) (Table 1).

Solid lipid NPs

Solid lipid NPs (SLNs) are composed of lipid samples that are solid at room temperature (Joshi and Müller 2009). According to findings, the SLNs are alternative drug delivery systems due to physical stability of the molecules and controlled drug release in specified amounts over a specified period of time. On the other hand, some limitations are associated with these NPs, such as poor nanodrug loading capacity, erratic availability of nanodrug in blood flow, and poor solubility in the lipid solutions (Wilczewska et al. 2012; Wissing et al. 2004).

A recent in vivo animal study indicated reduced size and weight of echinococcal cysts in secondary infection of CE treated with albendazole sulfoxide (ABZSO; 0.5 mg/kg) and ABZSO-loaded SLNs, but these reductions were not statistically significant (Ahmadnia et al. 2013).

Soltani et al. (2017) showed that ABZSO-loaded SLNs (2 mg/mL) have higher permeability and efficacy than ABZ alone on both fertile and infertile hydatid cysts in vivo. Moreover, the results obtained in a study by Jelowdar et al. (2017) demonstrated that the ABZ-loaded SLNs and Praziquantel (PZQ)-loaded SLNs reduced the size and weight of CE by 83% and 85%, respectively, while treatment with ABZ and PZQ alone decreased the weight and size of the cysts by 77.3% and 79%, respectively.

A recent in vitro and in vivo study indicated that ABZ-loaded SLNs at concentrations of 250 and 500 μg/mL have a higher protoscolicidal property (100% on day 5) than the free form of this drug (100% on day 7). However, only two

mice from the ABZ-loaded SLNs group did not have any cyst (Aminpour et al. 2019).

Liposome

Liposomes are small lipid vesicles formed by one or more layers of phospholipids around a water core. Consequently, liposomes can carry both hydrophobic and hydrophilic drugs in the nucleus or the phospholipid bilayers. Liposomes are used as a delivery system due to their flexible physicochemical and biophysical properties. However, some limitations are reported including erratic bioavailability in plasma and poor solubility (Akbarzadeh et al. 2013).

Lv et al. (2013) investigated the effects of a 2-mg/mL *Huaier* aqueous extract and 10 μg/mL liposomized albendazole (L-ABZ) against *E. granulosus*. The in vivo findings showed that the *H. aqueous* extract-ABZ combination was effective to reduce cyst development in treated mice, indicating 85% reduction in cyst weight, while the mortality rate of *E. granulosus* PSCs after in vitro exposure to L-ABZ + *H. aqueous* showed a significant scolicidal impact (100%) compared with that of L-ABZ alone (18%).

Another study on the therapeutic effects of different combinations of L-ABZ and/or cimetidine on rats infected with *E. multilocularis* indicated that oral administration of 35 mg/kg of L-ABZ increased the level of the drug in plasma, liver, and cyst compared with that of ABZ alone at 50-mg/kg dosage (Wen et al. 1996), in addition to the significant reduction in the biomass of metacestodes (75–94%). The synergistic interaction between ABZ and cimetidine increases the therapeutic effects of the drug on the experimental secondary infection of AE (Wen et al. 1996). Moreover, the administration of free and L-ABZ to mice infected with *E. multilocularis* PSCs had similar results in terms of the reduction of cysts' growth even until 4 weeks after delivering the final dose (10 mg/kg). Additionally, measurement of immunological parameters indicated that the anthelmintic effect of ABZ can be enhanced after being combined with liposomes due to the improvement of pharmacokinetics, and a considerable induction of Th1 response and effector functions of macrophages (Dvorožňáková et al. 2004).

L-ABZ formulations were successfully evaluated in a therapeutic regime of human AE in which 24 patients with multiorgan AE indicated that treatment with 10 mg/kg/day of L-ABZ had effective outcomes compared with the ones treated with ABZ alone (Li et al. 2013). Moreover, the administration of L-ABZ considerably improved the treatment efficacy of ABZ from 38 to 75%.

Lipid NPs

One of the drawbacks of liposomes is their insufficient capacity in encapsulation of hydrophobic drugs. Therefore, lipid nanocapsules (LNCs) are alternatively developed to encapsulate these lipophilic drugs. The LNCs are characterized by a hybrid structure between liposomes and polymeric NPs due to their oily core bound to an inflexible hard cover (Huynh et al. 2009). LNCs are designed to cover lipophilic drugs with no needs for organic solvents (Heurtault et al. 2002). LNCs deliver many drugs in a variety of ways, mostly parenteral (Lacoeuille et al. 2007). Pensel et al. (2015) formulated LNCs to improve ABZ bioavailability against CE in infected mice, indicating 91% cyst weight reduction, while only 47% reduction was observed in mice treated with ABZ.

Polymeric NPs

Polymeric NPs are solid colloidal nanometer particles in which the drug can be solved, absorbed, or encapsulated in a polymer matrix. These nanomaterials can be made from synthetic polymers such as polycaprolactone (PCL), polylactide (PLA), polyglycolide, poly(lactide-co-glycolide) (PLGA), and methoxy polyethylene glycol-polycaprolactone (mPEG-PCL), or natural compounds including alginate, insulin, or chitosan. Polymeric NPS are highly biocompatible and biodegradable. They can be produced in a variety of ways in large quantities and are excellent nanocarriers for the controlled and sustained release of drugs (Bhatia 2016; Prabhu et al. 2015). Characteristics of various polymeric NPs and their compounds in the treatment of CE and AE are shown in Tables 1 and 2. In an ex vivo study, Cong et al. (2008) indicated that penetrability and the ability of drug dispersion through the cyst membrane at various exposure times of ABZSO-loaded PLA were significantly higher than that of free ABZSO suspension.

De et al. (2012) demonstrated (in vitro) that the group treated with PZQ nanomaterial (polyisohexylcyanoacrylate-bound acrylate-bound doxorubicin and DL-lactide) exhibited significant ultrastructural changes and nucleosomal fragmentations in comparison with the ones treated with PZQ alone against CE.

Abulaihaiti et al. (2015) indicated that ABZ-loaded chitosan microspheres can effectively reduce the cyst weight (~ 94.5%) in mice infected with *E. multilocularis* after oral administration of drug. The effect of different concentrations of chitosan derived from *Penicillium waksmanii* and *P. citrinum*, and commercial chitosan (CC) at various time exposures on PSCs showed that the fungal chitosan, with a higher degree of deacetylation, had a stronger scolicidal activity. In addition, both types of chitosan exerted 100% scolicidal effects at 400-μg/mL dosage after an incubation time of 180 min (Fakhar et al. 2015). Similarly, the comparison of chitosan derived from *P. viridicatum* and *P. aurantiogriseum* with CC showed that the CC had a higher scolicidal activity and a higher degree of deacetylation (Rahimi-Esboei et al. 2013). Generally, the results indicated that fungal chitosan is more

effective than the CC in killing PSCs (Rahimi-Esboei et al. 2013). Torabi et al. (2018) have indicated that the chitosan-ABZ (ChABZ) plus chitosan-PZQ (ChPZQ) were more effective than the ABZ plus PZQ suspensions against *Echinococcus* cysts. In an in vitro experiment, no PSCs were revived on day 10 following the incubation with 5 and 10 μg/mL of ChABZ plus ChPZQ. Moreover, in an in vivo experiment, there was a considerable reduction in both the size and number of cysts in groups treated with ChABZ plus ChPZQ NPs (Torabi et al. 2018). A comparative in vitro study between ABZSO and ABZSO-loaded PLGA-PEG against *E. granulosus* PSCs indicated 100% scolicidal effect of ABZSO-loaded PLGA-PEG at very high concentrations of 150 and 200 μg/mL after 5 min of exposure, six times faster than that of ABZSO (after 30 min) (Naseri et al. 2016). Additionally, apoptotic activity measurement of ABZs and ABZ-loaded PLGA-PEG showed that caspase-3 mRNA expression in these two groups of drugs was higher than that in controls (Naseri et al. 2016). Farhadi et al. (2018) demonstrated that a flubendazole (FLBZ)-loaded mPEG-PCL was more effective than free FLBZ both in vitro and in vivo conditions. At the concentration of 10 μg/mL of FLBZ-loaded mPEG-PCL after 15 days, all the treated PSCs were killed in vitro, while the viability rate of the PSCs was only 44.0% following the treatment with 10 μg/mL free FLBZ. An in vivo study showed that the microcyst number decreased after 7 days of exposure to the FLBZ-loaded NPs at 10 μg/mL concentration (Farhadi et al. 2018).

An in vivo study showed that the anti-parasitic activity of 6-mg/kg ABZ-loaded PLA NPs i.v. against metacestodes of *E. multilocularis* was similar to that of 1500 mg/kg ABZ per os (Rodrigues Jr. et al. 1995). Moreover, the hepatic lesions and peritoneal metastasis rates also decreased compared with untreated mice.

Nanocrystals

Drug NCs are NPs with crystalline structure used to produce specific drugs stabilized by surfactants or polymeric stabilizers. Due to diminished particle size, they achieve higher solubility allowing the use of small doses in the treatment and reduction of the side effects of drugs (Junghanns and Müller 2008). Another study showed that the mean weight of cysts reduced by 50% in a group of mice receiving ABZ-loaded NC that was lower than that of the untreated mice infected with *E. multilocularis*, while the treatment with ABZ suspensions had no change in the mean weight of cysts (Pensel et al. 2018). The viability of PSCs in the ABZ-NC group was noticeably lower than that of controls. Furthermore, the clinical investigations indicated that both of the mentioned drug forms reduced the weight of cysts. Nevertheless, the mean weight of cysts remarkably reduced following the treatment with ABZ-NC compared with that of the controls (77%) (Pensel et al. 2018).

Future perspectives and conclusion

Currently, BMZ is the only approved drug for the treatment of human echinococcosis. Registering a new drug requires a great amount of time, resources, and money, which usually are not dedicated to such neglected tropical diseases. On the other hand, parasitostatic efficacy of ABZ is notably hampered by poor water solubility, resulting in low or erratic systemic bioavailability. An increased and stable bioavailability might mean decreasing the amount of drug used and duration of the treatment with a benefit for the patient in terms of possible adverse effects. The present review revealed that administration of various nanomaterials)NEs, NCs, and NPs(loaded with BMZs can considerably affect the scolicidal and cysticidal properties of BMZ compared with using BMZ alone. On the one hand, administration of the ABZ-loaded polymeric NPs was associated with a promising mortality rate for both PSCs and echinococcal cysts compared with that of other nanomaterials. However, the in vivo investigations showed changes in cyst weight and size, but the promising effect was attributed to the significant decrease in the cyst numbers. It is noteworthy that new formulations of drugs with parasiticidal properties should be tested in comparison with the efficacy of ABZ alone. Also, to increase the efficacy of these drugs, the human recommended doses should not be exceeded in the absence of toxicological studies and according to international agencies (i.e., EMA or FDA), the recommended doses of newly approved formulations should be determined for application in both preclinical and clinical settings. It was suggested that the *Echinococcus* spp. can develop through multiple phases in their biology. However, the targeting drugs are only effective on metacestode stages. As mentioned above, the suggested treatment is a combination of two or more nanodrugs (e.g., ABZS-loaded PLGA-PEG plus ChPZQ, ABZ-loaded PLA plus cimetidine, or ChABZ plus ChPZQ), particularly the ones with synergistic effects on stem cells of *Echinococcus*. Using synergistic features of the combined drugs can help to improve low solubility and poor absorption and decrease the toxicity associated with long-time administration of single drugs. The main problem with ABZ treatment is its hepatotoxicity that can occur in human patients. To overcome this problem, the periodic control of ABZSO levels in patients undergoing treatment is recommended. However, one of the limitations of the present review was the lack of assessing toxicity of BMZ-loaded nanocompounds against CE and AE both in vitro and in vivo. Therefore, to the best of authors' knowledge, one cannot decisively declare that NPs and ABZ-loaded NPs can reduce the hepatotoxicity in patients with CE. In the current

review, a number of studies applied nanodrugs/NPs with extremely high doses both in vitro and in vivo. Thus, to evaluate the clinical efficacy of nanocompounds, it is suggested to provide standard doses of ABZ-loaded NPs (15 mg/kg/day) in vivo.

Some evidence shows that the ABZSO enantiomers, (+)-(R)-ABZSO, can increase the affinity for cytosolic proteins of cestodes and increase solubility compared with that of ABZ in neurocysticercosis caused by *Taenia solium* infection (Paredes et al. 2013). Therefore, it can be concluded that the NP enantiomers ABZSO may remarkably improve the poor solubility and low bioavailability of ABZ in the therapeutic process.

In conclusion, the current review elucidates that BMZs loaded in various nanomaterials can affect the scolicidal and cysticidal properties compared with BMZ alone. In addition, BMZ-loaded polymeric NPs have a tendency to raise the mortality rate on PSCs and cysts compared with other nanomaterials. In the future, the use of the newly structured entities, attained by bridging ligands to the modified surface of NPs, as well as the electromagnetically produced nanodrugs would be helpful for developing fine-tuned formulations as an alternative to the already existing drugs against these neglected parasitic infections.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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