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Editorial Board Member of *World Journal of Hepatology*, Farzin Roohvand, PhD, Professor, Senior Scientist, Virology Department, Pasteur Institute of Iran, Tehran 13164, Iran. farzin.roohvand3@gmail.com

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*MINIREVIEWS*

# Current status of drug therapy for alveolar echinococcosis

Qin-Dong Jing, Ji-De A, Lin-Xun Liu, Hai-Ning Fan

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**Qin-Dong Jing, Lin-Xun Liu,** Department of General Surgery, Qinghai Provincial People's Hospital, Xining 810000, Qinghai Province, China

**Qin-Dong Jing,** School of Clinical Medicine, Qinghai University, Xining 810000, Qinghai Province, China

**Ji-De A,** Department of Hepatic Hydatidosis, Qinghai Provincial People's Hospital, Xining 810007, Qinghai Province, China

**Hai-Ning Fan,** Department of Hepatobiliary and Pancreatic Surgery, Qinghai Province Research Key Laboratory for Echinococcosis, Affiliated Hospital of Qinghai University, Xining 810001, Qinghai Province, China

**Co-first authors:** Qin-Dong Jing and Ji-De A.

**Co-corresponding authors:** Lin-Xun Liu and Hai-Ning Fan.

**Corresponding author:** Hai-Ning Fan, DPhil, Chief Physician, Professor, Department of Hepatobiliary and Pancreatic Surgery, Qinghai Province Research Key Laboratory for Echinococcosis, Affiliated Hospital of Qinghai University, No. 29 Tongren Road, Xining 810001, Qinghai Province, China. fanhaining@medmail.com.cn

## Abstract

Alveolar echinococcosis (AE) is a chronic zoonotic parasitic disease caused by infection with *Echinococcus multilocularis*. AE is associated with a high mortality rate and poses a significant threat to human health. The primary treatment for AE is surgical resection of the lesions; however, owing to its long incubation period and insidious disease progression, many patients are diagnosed only after the onset of complications such as liver cirrhosis, jaundice, and portal hypertension, which preclude curative surgical intervention. For patients who are unwilling or unable to undergo surgery, lifelong administration of anti-AE medications is necessary. Benzimidazole compounds, such as albendazole and mebendazole, are the current mainstays of treatment, offering good efficacy. Nevertheless, these medications primarily inhibit parasite proliferation rather than eradicate the infection, and their long-term use can lead to significant drug-related toxic effects. Consequently, there is an urgent need to develop new therapeutic strategies that convey better efficacy and reduce the adverse effects associated with current treatments. Recent advancements in AE therapy include novel synthetic compounds such as antiviral agents, antibiotics, antineoplastic agents, immunosuppressants, and antiangiogenic agents, as well as natural compounds derived from traditional Chinese and Tibetan medicine. These new drugs show promising

clinical potential because they interfere with parasitic metabolic pathways and cellular structures. This review aims to discuss recent research on AE drug therapy, including mechanisms of action, dosing regimens, signalling pathways, and therapeutic outcomes, with a goal of providing new insights and directions for the development of anti-AE drugs and summarizing current advancements in AE pharmacotherapy.

**Key Words:** Alveolar echinococcosis; Drug therapy; Albendazole; Synthetic compounds; Natural compounds



**Core Tip:** Our manuscript reviews the research on albendazole and other drugs in the treatment of alveolar echinococcosis (AE), with a particular focus on anti-angiogenic drugs, immunosuppressants, and the role of the immune microenvironment in AE. These areas represent significant parts of our manuscript and are currently in the exploratory phase, so extensive basic validation experiments are still needed.

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## INTRODUCTION

Echinococcosis is a severe zoonotic disease that poses a considerable threat to human health. It is caused by larval infection with the *Echinococcus tapeworm*[1]. The adult tapeworm primarily resides in the small intestinal mucosa of carnivorous animals such as dogs, wolves, and foxes. In contrast, its larvae infect herbivorous animals, including humans, cattle, and sheep, *via* egg ingestion, leading to organ pathologies, primarily of the liver, and, in severe cases, can also affect the lungs, brain, and other organs[2]. Echinococcosis is distributed worldwide, and the two most significant types are cystic echinococcosis (CE), caused by *Echinococcus granulosus* (*E. granulosus*) larvae, and alveolar echinococcosis (AE), caused by *Echinococcus multilocularis* (*E. multilocularis*) larvae. CE is relatively common and is characterized by the formation of fluid-filled cysts that contain numerous larval parasites[3]. The prognosis for CE is relatively favourable, especially when early diagnosis and treatment are available. Surgical excision of the cysts combined with pharmacotherapy can effectively manage the disease. AE, conversely, is characterized by invasive growth that resembles malignant tumours, which primarily invade the liver but are also capable of spreading to the lungs, brain, and other organs[4]. The prognosis for AE is poor, with a high mortality rate[5]. The primary treatment for AE is surgical resection of the lesions. However, owing to its aggressive and metastatic nature, many patients are diagnosed at a stage where surgical intervention is no longer feasible or the lesions cannot be completely removed[6]. Consequently, pharmacotherapy is critically important. Currently, benzimidazole compounds such as albendazole and mebendazole are the mainstay treatments for AE[7]. These drugs are effective but primarily inhibit parasite proliferation rather than killing parasites outright. Long-term treatment, which can lead to significant toxic effects such as hepatotoxicity and bone marrow suppression, is often needed. Furthermore, the cessation of treatment often results in high recurrence rates due to the inability of these drugs to completely eradicate the parasites, highlighting the urgent need for more effective alternative drug therapies[8]. Recent advances in the understanding of AE pathophysiology have spurred the development of new drugs and treatment strategies. Numerous compounds, including antineoplastic drugs, antibiotics, antiangiogenic agents, and natural compounds derived from traditional Chinese and Tibetan medicine, are being tested *in vitro* and *in vivo*. Benzimidazole combination therapies with other drugs are also being explored at an increasing rate, although only a few have reached clinical application[9]. This review discusses various drug trials regarding AE, including the mechanisms of action and therapeutic outcomes of the drugs, with the aim of providing new perspectives and directions for AE drug development and summarizing recent progress in AE pharmacotherapy.

## BENZIMIDAZOLES

Since its introduction in 1961, the benzimidazole class of drugs has been pivotal in the treatment of parasitic infections, including AE[10]. These drugs not only have achieved significant success as antiparasitic therapies but also have demonstrated efficacy in treating various conditions, such as cancer, inflammation, and tuberculosis[11]. Benzimidazoles exert their antiparasitic effects primarily by disrupting the microtubule structures of parasites, thereby inhibiting their cellular division and metabolism. Additionally, these drugs interfere with glucose uptake during the parasitic larval stage, leading to glycogen depletion and degenerative changes in mitochondria and the endoplasmic reticulum[12]. Among the benzimidazole family, albendazole and mebendazole are the main drugs approved for the treatment of echinococcosis in humans and are listed on the World Health Organization's essential medicines list owing to their

significant antiparasitic properties[13,14]. This chapter focuses on the combined use of albendazole with other drugs in the treatment of AE, highlighting the potential for enhanced therapeutic efficacy and reduced toxicity.

## COMBINATION THERAPY WITH ALBENDAZOLE

Recent studies[15] have highlighted the potential of ubenimex, a broad-spectrum inhibitor of leucine aminopeptidase, in conjunction with albendazole for treating AE. This combination therapy has demonstrated significant efficacy in reducing tumour growth and infiltration in murine models infected with *E. multilocularis*, as well as mitigating liver damage. However, its impact on the growth and development of the parasite remains limited. Research suggests that immunisation with *E. multilocularis* leucine aminopeptidase can induce a specific immune response that inhibits the invasion of the parasite[16]. Re-evaluation studies have shown that ubenimex can similarly inhibit the invasion of *E. multilocularis*[17]. Based on these findings, the combination of ubenimex and albendazole shows enhanced efficacy in treating AE, although the precise mechanisms of this combined therapy require further investigation. Additionally, researchers have reported[18] that combining carvacrol, a monoterpenoid phenol, with albendazole results in superior therapeutic efficacy in both *in vitro* and *in vivo* models compared with albendazole monotherapy. This combination can enhance treatment outcomes without necessitating an increase in albendazole dosage or an extension of the treatment period. Moreover, combining metformin with a low dose of albendazole has been shown to enhance the therapeutic efficacy of existing high-dose albendazole monotherapy. This combination not only improves treatment outcomes but also reduces drug-induced toxicity to some extent[19].

Owing to the poor solubility and bioavailability of albendazole, various solubilizing agents have been developed to increase its efficacy. Notable examples include the albendazole crystal dispersion system, albendazole hydrochloride-hydroxypropyl methylcellulose phthalate composite, and albendazole hydroxyethyl sulfonate-hydroxypropyl methylcellulose phthalate composite. *In vivo* studies have demonstrated that these albendazole complexes exhibit superior pharmacokinetic properties compared with those of conventional albendazole, and *in vitro* studies have shown significantly improved efficacy over that of conventional albendazole[20]. Atovaquone, an antimalarial drug, has been identified as a potent inhibitor of the mitochondrial complex in *E. multilocularis*. *In vitro* studies have revealed that the combination of atovaquone with albendazole under aerobic conditions facilitated more rapid clearance of the parasite. Furthermore, *in vivo* studies indicated that this combination significantly reduced the sizes of hepatic lesions in mice, demonstrating superior efficacy compared with albendazole monotherapy.

Recent studies have demonstrated that the combination of albendazole with thymol has superior therapeutic efficacy to monotherapy in the treatment of AE[21].

Thymol, a monoterpene phenol, enhances the antiparasitic effect of albendazole, likely because of its ability to disrupt parasite cell membranes and induce apoptosis[22]. 2-deoxy-D-glucose (2-DG), a glucose analogue that inhibits glycolysis has also been shown to significantly impair the growth and development of *E. multilocularis* larvae. Research has indicated that the combined use of 2-DG and albendazole *in vivo* mouse models results in a marked increase in therapeutic efficacy. This combination potentially disrupts the parasite's energy metabolism, leading to increased mortality rates among the parasites[23]. Furthermore, early studies[24] revealed that the combination of nitazoxanide, an antiparasitic agent known for its broad-spectrum activity, with albendazole results in promising antiparasitic effects in vitro. Nitazoxanide is suggested to inhibit the pyruvate oxidoreductase pathway, which is crucial for anaerobic energy metabolism in *Echinococcus* species. Additionally, glucan supplemented with zinc has emerged as an effective adjunct to albendazole therapy. The supplementation of zinc, an essential trace element, combined with glucan, a polysaccharide, is proposed to increase the host immune response while enhancing the antiparasitic effects of albendazole, making it a preferred treatment strategy for AE[25]. These findings highlight the potential of combination therapies in enhancing the efficacy of albendazole for the treatment of AE. Future research should focus on elucidating the precise mechanisms of these therapeutic combinations and conducting clinical trials to validate their efficacy and safety in human subjects. The contents of combination therapies with albendazole are described in Table 1.

## ANTIANGIOGENIC DRUGS

The development and pathogenesis of parasites within the host are heavily reliant on the nutrient supply. The formation of new blood vessels around the parasite likely provides necessary nutrients and serves as a conduit for metastasis[26]. In addition to the host immune system, an insufficient blood supply is a critical factor leading to the death of parasites within the host. Therefore, antiangiogenic therapy offers a promising new avenue for the treatment of AE. Anacardic acid (AA), a compound found in cashew nut shells, has been demonstrated to have significant antitumour[27] and antiparasitic[28] effects. To better elucidate the therapeutic potential and underlying mechanisms of AA in AE treatment, both *in vivo* and *in vitro* studies have been conducted. These studies[29] have revealed that AA inhibits AE progression primarily through the suppression of angiogenesis by inhibiting the expression of the vascular endothelial growth factor (VEGF)-induced signalling pathway. These findings indicate that AA could effectively restrict the nutrient supply essential for parasite growth and metastasis. Additionally, other studies[30] have shown that the antiangiogenic drug sunitinib can inhibit AE progression by blocking VEGF-A-induced angiogenesis. The inhibition of the fibroblast growth factor signalling pathway may be another crucial mechanism, as this pathway is vital for the survival of parasitic stem cells[31]. Sorafenib, a novel multitarget antineoplastic agent, also has potential in the treatment of AE. Its mechanisms of action include direct inhibition of tumour cell proliferation by blocking the fibrosarcoma protein/mitogen activates

**Table 1 The contents of the combination therapy with albendazole**

| Treatment plan | *In vitro* or *invivo* | Treatment effect |
|---|---|---|
| ABZ + ubenimex | *In vitro* + *in vivo* | Better therapeutic effect |
| ABZ + carvacrol | *In vitro* + *in vivo* | Better therapeutic effect |
| ABZ + metformin | *In vitro* + *in vivo* | Better therapeutic effect |
| ABZ + atovaquone | *In vitro* + *in vivo* | Better therapeutic effect |
| ABZ + thymol | *In vitro* + *in vivo* | Better therapeutic effect |
| ABZ + 2-DG | *In vitro* | Better therapeutic effect |
| ABZ + nitazoxanide | *In vitro* | Has a certain effect |
| ABZ + GIZn | *In vitro* + *in vivo* | Has a certain effect |
| ABZ solubilizing agents | *In vitro* + *in vivo* | Better therapeutic effect |

ABZ: Albendazole; 2-DG: 2-deoxy-D-glucose; GIZn: Glucan supplemented with zinc.

extracellular signal-regulated kinases/extracellular signal regulated kinase signalling pathway and indirect suppression of tumour growth by preventing new blood vessel formation through the inhibition of VEGF receptors (VEGFRs) and platelet-derived growth factor receptors[32]. Our previous studies have revealed that sorafenib has significant anti-AE efficacy in a rat model, potentially through the inhibition of VEGFR, which consequently blocks the formation of new blood vessels around the lesion, thereby inhibiting AE progression. These findings suggest that antiangiogenic therapy may serve as a potential pharmacological target for the treatment of AE, offering new hope for managing this challenging disease.

## ANTITUMOUR DRUGS

As early as the 1970s, researchers began investigating the potential application of anti-tumour drugs in the treatment of AE[33]. Certain cytostatic drugs, which were originally designed for cancer treatment, can interfere with the metabolic processes and cell cycles of parasites, thereby inhibiting their growth and reproduction[34,35]. The mechanisms of action of these drugs may include the inhibition of cell proliferation-related signalling pathways, the induction of parasitic cell apoptosis, and a reduction in the energy supply to parasitic cells. Imatinib (a small-molecule protein kinase inhibitor widely used for the treatment of chronic leukaemia and malignant gastrointestinal stromal tumours) has been shown to effectively inhibit the growth of *E. multilocularis* larvae, suggesting its potential as a chemotherapeutic agent for AE[36]. Bortezomib (a drug used for the treatment of multiple myeloma and mantle cell lymphoma)[37,38] has demonstrated high efficacy *in vitro*; however, it has not achieved the expected outcomes in mouse models *in vivo*[39]. These findings indicate that the proteasome targeted by bortezomib could be a potential therapeutic target for AE, but further investigation is needed to understand its *in vivo* efficacy. 2-methoxyestradiol (2-ME2) is an effective anti-tumour drug used to treat breast cancer[40]. *In vitro* studies have shown that 2-ME2 has significant antiparasitic effects against *E. multilocularis*, and promising results have been demonstrated in mouse models. However, compared with those of albendazole, the treatment outcomes did not significantly differ, suggesting that the effects of 2-ME2 might be related to the reduction in 14-3-3 protein expression[41].

Three-bromopyruvate (3-BrPA) is a potential anti-tumour agent that is known primarily for its ability to selectively kill cancer cells by inhibiting the glycolytic pathway[42]. In both *in vitro* and *in vivo* experiments regarding the treatment of AE, 3-BrPA has demonstrated significant therapeutic efficacy. Notably, *in vivo* studies using mouse models have shown that 3-BrPA has minimal hepatotoxicity. Given that AE patients almost invariably suffer from hepatic involvement, this characteristic renders 3-BrPA a promising candidate for AE treatment[43]. Furthermore, these findings suggest that glycolytic enzymes may serve as potential therapeutic targets for AE. Genistein, a phytoestrogen found in plants, is known to prevent various cancers and cardiovascular diseases[44]. *In vitro* studies regarding AE, genistein has exhibited notable antiparasitic activity. However, long-term use of genistein could induce oestrogenic effects, which necessitates caution. To mitigate this issue, researchers have employed synthetic genistein *in vitro* experiments, which has demonstrated significant antiparasitic efficacy with considerably decreased oestrogenic side effects due to the knockout of expression of key genes. The proposed mechanism of action involves the inhibition of tyrosine protein kinase, but further *in vivo* studies are needed to confirm these effects[45]. Lonidamine, a broad-spectrum anti-tumour drug, has shown marked antiparasitic activity in *in vitro* studies on AE, indicating its potential as a therapeutic agent[46].

Previous studies have demonstrated that doxorubicin can effectively reduce the viability and developmental progression of *E. multilocularis* in both *in vivo* and *in vitro* models[47]. This reduction suggests the significant potential of doxorubicin in disrupting the metabolic and proliferative processes of the parasite, thereby impeding its lifecycle and reducing its pathogenicity. Other anti-tumour agents, including tamoxifen[48], 5-fluorouracil[49], and paclitaxel[34], have shown notable antiparasitic effects in studies focused on CE caused by *E. granulosus*. These findings indicate that these

drugs may disrupt key cellular functions necessary for parasitic survival and development. Given their mechanisms of action, such as inhibiting life cycle progression and inducing apoptosis, these drugs may also hold promise for treating AE, pending further research to assess their efficacy against *E. multilocularis*. Conversely, some anti-tumour drugs, such as nilotinib and everolimus, have not demonstrated significant therapeutic effects against AE[50]. This observation highlights the importance of identifying specific molecular targets within the parasite that are essential for its life cycle, which may differ from those in tumour cells. Understanding these unique pathways is crucial for developing effective treatment strategies for AE. The repurposing of anti-tumour drugs for AE treatment offers a promising avenue, particularly as these drugs can interfere with cellular processes that are essential for the survival of parasitic organisms. However, the variability in drug efficacy highlights the importance of understanding the unique biology of *E. multilocularis* and identifying specific targets that can be exploited for therapeutic intervention. Further *in vivo* studies are crucial to confirm the potential of these anti-tumour agents and to facilitate their integration into clinical strategies for managing AE.

## IMMUNOSUPPRESSANTS

In recent years, immunotherapies such as immune checkpoint blockade have achieved significant advancements in cancer treatment[51]. Because AE shares similar characteristics with cancer in terms of invasiveness and metastasis, interest in applying immunotherapy to parasitic diseases has increased. *E. multilocularis* infection is primarily modulated by the host adaptive immune response[52]. Studies have indicated that infection with *E. multilocularis* in mice induces alternative activation of macrophages, which is closely linked to the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) signalling pathway[53]. Consequently, researchers have explored the use of monoclonal antibodies (MAbs) to block the PD-1/PD-L1 pathway *in vitro* and *in vivo* experiments regarding AE, and these have demonstrated significant antiparasitic effects[54]. Additional studies have reported that the PD-1/PD-L1 pathway primarily combats *E. multilocularis* infection by modulating adaptive and innate immune cells[55], suggesting that the PD-1/PD-L1 pathway could be a potential therapeutic target for the treatment of AE.

T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) is an emerging immunosuppressive receptor. Research[56] has shown that anti-TIGIT MAbs can increase the synthesis of interferon-gamma (IFN-γ) and tumour necrosis factor-alpha by natural killer (NK) cells. Immunotherapy using TIGIT MAbs in mice infected with *E. multilocularis* has demonstrated the potential to reverse NK cell exhaustion, thereby enhancing the immune response and effectively inhibiting lesion growth. These findings offer a new perspective on immunotherapy for AE. Previous studies have indicated that treatment with IFN-γ, IFNα-2α, and interleukin-12 has partial efficacy against AE, likely due to immunomodulatory effects[57-59]. However, like the treatment of AE with anticancer drugs, the immunosuppressant cyclosporin A does not appear to have anti-*E. multilocularis* activity, possibly because of its role in mediating immune response mechanisms[60]. Overall, immunotherapy represents a promising avenue for treating AE, yet more research into MAbs and immune checkpoint inhibitors is needed to substantiate these findings.

## ANTI-INFECTIVE DRUGS

Amphotericin B is an antifungal agent that has shown promising results in cases in which AE patients in terminal stages have developed resistance to albendazole. Case reports have suggested that amphotericin B treatment yields favourable outcomes for such patients[61,62], and both *in vitro* and *in vivo* studies have confirmed its efficacy in inhibiting the growth of *E. multilocularis*. However, it does not exhibit direct parasiticidal activity, necessitating prolonged treatment for patients[63]. Compared with albendazole, pseudolaric acid B, a compound with antifungal properties, has been demonstrated to have a potent inhibitory effect on *E. multilocularis* both *in vitro* and *in vivo*, with a lower toxicity profile. These findings indicate that pseudolaric acid B might be a potential chemotherapeutic agent for treating AE[64]. Itraconazole has been proven to effectively inhibit the growth of *E. multilocularis*, although its action appears to be limited to growth inhibition rather than parasiticidal effects[65]. Clarithromycin, a macrolide antibiotic, has shown variable effects on *E. multilocularis in vitro*, including a loss of motility in larvae following treatment, thereby hindering their growth and development[66]. Buparvaquone, a quinone compound with antibacterial activity, has been shown to exert early antiparasitic effects by damaging the mitochondria of *E. multilocularis*; however, its overall efficacy has yet to be fully validated[67]. The application of anti-infective drugs, including antibacterial, antifungal, and antiviral agents, presents new avenues for AE treatment, although extensive research is needed to establish their efficacy and safety.

## ANTIMALARIAL DRUGS AND INSECTICIDES

Mefloquine, a classic antimalarial drug, was shown in early studies to inhibit the proliferation of *E. multilocularis* both *in vivo* and *in vitro*[68]. However, it does not exhibit direct parasiticidal activity and may induce severe psychiatric side effects, limiting its use; however, it could be a salvage therapy option for terminal-stage patients[69]. Recent research[70] has indicated that four mefloquine derivatives can significantly reduce drug-related damage. Although their anti-*E. multilocularis* activities are not markedly superior to that of mefloquine, these derivatives offer improved therapeutic choices for AE. Artemisinin, now a first-line antimalarial treatment, along with its derivatives[71], has shown good

activity against *E. multilocularis* in vitro, although there is no significant difference compared with albendazole[72]. Thiacloprid, a novel insecticide, has demonstrated parasiticidal effects against *E. multilocularis* in both *in vivo* and *in vitro* studies, suggesting that it could be a promising new treatment for AE[73]. Carbazole aminoalcohols, which are broad-spectrum antiparasitic agents that are effective against *Plasmodium falciparum* and *Schistosoma japonicum*[74], have shown significant therapeutic effects *in vitro* against *E. multilocularis*. *In vivo* studies have revealed a marked reduction in tumour mass in mice, indicating that carbazole aminoalcohols could be a potential therapeutic option for AE[75]. The anthelmintic drugs triclabendazole and clorsulon have also demonstrated good anti-*E. multilocularis* effects *in vitro*[76].

## OTHER SYNTHETIC COMPOUNDS AND DRUG CARRIERS

Verapamil, a calcium channel blocker commonly used to treat cardiovascular diseases, has been shown to have inhibitory effects on *E. multilocularis* by downregulating calcium ion levels both *in vivo* and *in vitro*[77]. These findings suggest that calcium ion signalling pathways could be potential therapeutic targets for AE and that verapamil might represent a novel anti-AE drug. Scholars have also investigated the effects of dithiocarbamate derivatives and disulfiram on *E. multilocularis via* both *in vivo* and *in vitro* experiments. Dithiocarbamate derivatives exhibit significant antiparasitic effects[78]. Interestingly, while disulfiram has shown antiparasitic activity in previous studies, it did not display anti-*E. multilocularis* activity in the present study[79]. In the pharmacological treatment of AE, a major challenge for clinicians and patients is low drug exposure levels *in vivo*, leading to suboptimal therapeutic efficacy. This highlights the urgent need for new drug delivery systems that can target the most affected organs and increase *in vivo* drug exposure. Studies have shown that polylactic-co-glycolic acid nanoparticles, when loaded with anti-AE drugs, significantly improved therapeutic outcomes and reduced drug toxicity in a murine model[80]. Another study combined magnetic inorganic particles with anti-AE drugs to form composite microspheres with magnetic properties and specific structures for drug delivery. These magnetic microspheres demonstrated significant parasiticidal effects in mice[81]. These findings suggest that targeted drug delivery systems could be a promising strategy for the treatment of AE. The efficacy of various synthetic compounds against AE is shown in Table 2.

## NATURAL COMPOUNDS

For many years, natural compounds have been regarded as a significant repository for drug development[82]. Compared with synthetic compounds, natural compounds often exhibit milder adverse drug reactions[83]. Herbal medicines are also extensively used in antiparasitic research. For example, asparagusic acid, a natural compound extracted from asparagus, has been shown to exert antiparasitic effects by inducing apoptosis in tissues surrounding lesions. Its potential mechanisms of action include regulating mitochondrial membrane potential levels in *E. multilocularis* and modulating the phosphoinositide 3-kinase/protein kinase B signalling pathway[84]. Another natural compound, crocin, a water-soluble carotenoid, has demonstrated potential in inhibiting the activity of *E. multilocularis* both *in vivo* and *in vitro*. It is considered a promising alternative treatment for AE[85]. Allicin, one of the main active components of garlic, not only possesses antibacterial[86], anti-tumour[87], and anti-parasitic[88] properties but also has been shown to exhibit significant anti-*E. multilocularis* activity by enhancing immune responses[89]. Furthermore, the essential oil of *Thymus capitatus*, a natural spice produced in regions such as Spain, has been found to have good anti-*E. multilocularis* activity *in vitro*. However, its specific mechanism of action and targets have not yet been fully elucidated[90].

Ampelopsin, a natural compound commonly used in cancer therapy, has been found to exhibit significant *in vitro* inhibitory effects on *E. multilocularis* and shows no obvious toxicity at effective doses[91]. Menthol, a major component of plant essential oils, possesses important pharmacological properties. Both menthol and its prodrug, menthol-pentanol, have demonstrated strong antiparasitic activities against *E. multilocularis* in both *in vivo* and *in vitro* studies, with menthol-pentanol exhibiting more efficient parasiticidal effects than menthol[92]. Osthole, a compound extracted from plant fruits, has shown promising anti-*E. multilocularis* activity both *in vivo* and *in vitro*, making it a potential candidate for therapeutic application[93]. Additionally, various natural compounds, such as *Punica granatum* peel extract, matrine, and curcumin, have demonstrated significant inhibitory and parasiticidal effects on *E. multilocularis* in both *in vivo* and *in vitro* experiments[94]. Their antiparasitic mechanisms may include the inhibition of protein synthesis, the induction of apoptosis, and interference with energy metabolism. Despite the significant antiparasitic effects observed in recent *in vivo* and *in vitro* studies, further validation is needed to confirm their clinical applicability. The efficacy of various natural compounds against AE is shown in Table 3.

## CONCLUSION

Currently, AE remains a significant challenge for surgeons. For patients who cannot undergo surgery or choose not to undergo surgery, benzimidazole derivatives, particularly albendazole, remain the primary treatment options. However, long-term use of benzimidazole drugs can lead to serious adverse effects, and some patients may develop resistance, posing additional therapeutic challenges. Recent studies have demonstrated that antiangiogenic agents, immunosuppressants, anticancer drugs, anti-infective drugs, antimalarials, insecticides, natural compounds such as herbal medicines, and nanomedicine delivery systems exhibit substantial potential in the treatment of AE. Combination therapies and

**Table 2 Synthetic compounds for anti-alveolar echinococcosis therapy**

| Treatment plan | | *In vitro* or *invivo* | Treatment effect |
|---|---|---|---|
| Anti-angiogenic drugs | Anacardic acid | *In vitro* + *in vivo* | Inhibit AE progression |
| | Sunitinib | *In vitro* + *in vivo* | Inhibit AE progression |
| | Sorafenib | *In vivo* | Inhibit AE progression |
| Anti-tumour drugs | Imatinib | *In vitro* | Inhibit *E. multilocularis* growth |
| | Bortezomib | *In vitro* + *in vivo* | Inhibit *E. multilocularis* growth |
| | 2-ME2 | *In vitro* + *in vivo* | Better therapeutic effect |
| | 3-BrPA | *In vitro* + *in vivo* | Better therapeutic effect |
| | Genistein | *In vitro* | Inhibit *E. multilocularis* growth |
| | Lonidamine | *In vitro* | Inhibit *E. multilocularis* growth |
| | Doxorubicin | *In vitro* + *in vivo* | Better therapeutic effect |
| | Tamoxifen | *In vitro* + *in vivo* | Better therapeutic effect |
| | 5-fluorouracil | *In vitro* + *in vivo* | Better therapeutic effect |
| | Paclitaxel | *In vitro* + *in vivo* | Better therapeutic effect |
| | Nilotinib | *In vitro* | No therapeutic effect |
| | Everolimus | *In vitro* | No therapeutic effect |
| Immunosuppressants | PD-1/PD-L1 MAbs | *In vitro* + *in vivo* | Better therapeutic effect |
| | TIGIT MAbs | *In vitro* + *in vivo* | Better therapeutic effect |
| | IFN-γ | *In vitro* | Inhibit *E. multilocularis* growth |
| | IFNα-2α | *In vitro* | Inhibit *E. multilocularis* growth |
| | IL-12 | *In vitro* | Inhibit *E. multilocularis* growth |
| | Cyclosporin A | *In vitro* | No therapeutic effect |
| Anti-infective drugs | Amphotericin B | *In vitro* + *in vivo* | Better therapeutic effect |
| | Pseudolaric acid B | *In vitro* + *in vivo* | Better therapeutic effect |
| | Itraconazole | *In vitro* | Inhibit *E. multilocularis* growth |
| | Macrolide antibiotic clarithromycin | *In vitro* | Inhibit *E. multilocularis* growth |
| | Buparvaquone | *In vitro* | Inhibit *E. multilocularis* growth |
| Antimalarial drugs and insecticides | Mefloquine | *In vitro* + *in vivo* | Better therapeutic effect |
| | Artemisinin | *In vitro* | Inhibit *E. multilocularis* growth |
| | Thiacloprid | *In vitro* + *in vivo* | Better therapeutic effect |
| | Carbazole aminoalcohols | *In vitro* + *in vivo* | Better therapeutic effect |
| | Triclabendazole | *In vitro* | Inhibit *E. multilocularis* growth |
| | Clorsulon | *In vitro* | Inhibit *E. multilocularis* growth |
| Other synthetic compounds and drugs carriers | Verapamil | *In vitro* + *in vivo* | Better therapeutic effect |
| | Dithiocarbamate Derivatives | *In vitro* | Inhibit *E. multilocularis* growth |
| | PLGA | *In vivo* | Better therapeutic effect |

IL-12: Interleukin-12; PLGA: Polylactic-co-glycolic acid; 2-ME2: 2-methoxyestradiol; 3-BrPA: 3-bromopyruvate; PD-1: Programmed cell death protein 1; PD-L1: Programmed cell death ligand 1; MAbs: Monoclonal antibodies; TIGIT: T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain; IFN: Interferon; AE: Alveolar echinococcosis.

**Table 3 Natural compound anti-alveolar echinococcosis therapy**

| Treatment plan | *In vitro* or *invivo* | Treatment effect |
|---|---|---|
| Asparagusic acid | *In vitro* + *in vivo* | Better therapeutic effect |
| Crocin | *In vitro* + *in vivo* | Better therapeutic effect |
| Allicin | *In vitro* + *in vivo* | Better therapeutic effect |
| Thymus capitatus essential oil | *In vitro* | Inhibit *E. multilocularis* growth |
| Ampelopsin | *In vitro* | Inhibit *E. multilocularis* growth |
| Menthol | *In vitro* + *in vivo* | Better therapeutic effect |
| Osthole | *In vitro* + *in vivo* | Better therapeutic effect |
| Punica granatum peel extract | *In vitro* + *in vivo* | Better therapeutic effect |
| Matrine | *In vitro* + *in vivo* | Better therapeutic effect |
| Curcumin | *In vitro* + *in vivo* | Better therapeutic effect |

emerging drugs such as corticosteroids also provide new directions and possibilities for treating AE. Although existing drug therapies have led to some progress in controlling AE, issues of drug resistance and toxicity from prolonged use remain major challenges. Future research should focus on developing new therapeutic strategies, exploring optimal drug combinations to increase treatment efficacy, and reducing side effects to bring new hope to AE patients.

## FOOTNOTES

**Author contributions:** Jing QD and A JD conceptualized and designed this research and obtained, analyzed, interpreted data, and prepared the initial draft of the manuscript, both authors have made crucial and indispensable contributions to the completion of the project, and therefore qualify as co first authors of the paper; Liu LX and Fan HN conducted a critical review of the important knowledge content in the manuscript, as co corresponding authors, they played an indispensable role in data interpretation and manuscript preparation; Fan HN conceptualized, designed, and supervised the entire process of the project; All the authors have read and approved the final manuscript.

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**Country of origin:** China

**ORCID number:** Qin-Dong Jing 0009-0009-2857-2143; Ji-De A 0000-0003-4478-1972; Lin-Xun Liu 0000-0003-1998-5746; Hai-Ning Fan 0000-0002-1796-5891.

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