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Natural products applied against hydatid cyst protoscolices: A review of past to present

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ABSTRACT

Echinococcus granulosus is the causative agent of cystic echinococcosis (CE), which is distributed all around the world. CE is one of the most important global parasitic infectious diseases, both in humans and animals. This parasite causes hydatid cysts that can be lodge at different organs of host such as liver, lung even in heart and brain which may lead to death. Presently, numerous scolicidal chemical agents have been administrated for inactivation of the hydatid cyst contents. Because of increasing resistance and adverse effects of medications include abnormalities of liver function, abdominal pain, diarrhea, nausea, vomiting, dizziness, and headache; there is a need to find alternative therapies either with the least or without side effects. Recently, there is a high tendency among researchers to evaluate and present herbal plants as alternative option due to being inexpensive, easy available, low side effects and toxicity. Till now, many efforts have been conducted on herbal extracts against protoscolices of hydatid cysts throughout the world. Therefore, the current review systematically searched the following electronic databases: PubMed, Science Direct, Scopus, and Google Scholar on published papers according to the keywords. In addition, a comprehensive list of medicinal plants was prepared and some of these herbal plants which showed the best efficacy and promising results are discussed elaborately.

1. Introduction

Humans have acquired a remarkable number of parasites, including protozoan (over 70 species), helminthes (about 300 species), and arthropod parasites (Cox, 2002). The parasitic helminthes infections are considered neglected tropical diseases that receive less than 1% of global research dollars. Nowadays, it is estimated that roughly one-third of the population approximately three billion people that live in low socioeconomic status in developing areas of sub-Saharan Africa, Asia, and the Americas are infected with one or more helminthes (Hotez et al., 2008). There are two major phyla of helminthes including the Nematodes (also known as roundworms) and the Platyhelminthes (Trematoda and Cestoda) (Hotez et al., 2008). *Echinococcus* species in terms of pathogenicity are the most important Cestodes. From six recognized *Echinococcus* species, *Echinococcus granulosus* causing cystic echinococcosis (CE), *E. multilocularis* causing alveolar echinococcosis, *E. vogeli* and *E. oligarthrus* causing polycystic echinococcosis are of public health concern. In addition *E. shiquicus* and *E. felidis* two new species have recently been identified, but their zoonotic transmission potential is unknown (Eckert and Deplazes, 2004). Among them, CE is a cosmopolitan zoonosis with extremely endemic areas especially it is prevalent in regions of South America, North Africa, China, and the Middle East (Harandi et al., 2012). Currently there are three treatment options for CE: surgery, ultrasound-guided aspiration, and chemotherapy. The recommended chemotherapy drugs for treatment of hydatidosis are benzimidazole derivatives, such as mebendazole and albendazole. However, due to increase of their resistance protoscolices to and drug side effects, their use are limited (Naseri et al., 2016; Walker et al., 2004b). So, many efforts have been made to discover new antimicrobial compounds from various types of sources such as plants and microorganisms. For many centuries, herbal remedies and plant extracts have been used as treatments for ailments from headaches to parasite infections (Anthony et al., 2005). Only in

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the past three decades, scientists have seriously initiated to determine the efficacy of plant-derived traditional remedies and their mode of actions. Considering the side effects of anti-hydatid drugs and the severity of hydatidosis, knowledge for the treatment of parasitic infections, it is necessary to investigate on new anti-hydatid compounds with high activity, low toxicity that are cheaper and have more efficacies. Therefore, in this review we prepared a list of all natural products which were used against hydatid protoscolices. Also extracts with the best results were discussed elaborately.

2. Etiology

The life cycle of *E. granulosus* (Cestoda; Taeniidae) contains dogs and other canids as definitive hosts (intestinal stage), as well as domestic and wild animals as intermediate hosts (larval stage) (Moro and Schantz, 2009; Thompson, 1995). The adult worms, which are less than 7 mm in length, dwell in the small intestine of proper canids, lay eggs and defecated with the faeces of the animal and contaminate the environment broadly (Rahimi et al., 2016; Romig, 2003). Susceptible intermediate host that accidentally ingest infective eggs develop the parasite's larval stage. Humans are considered dead end host that does not play a role in the natural cycle of the parasite (Sarvi et al., 2014; McManus et al., 2003). Larval stages (hydatid cysts) develop in the liver, lungs and infrequently other organs. Hydatid cyst contains two parasite-derived layers; an inner nucleated germinal layer and an outer acellular laminated layer surrounded by a host-produced fibrous capsule as the consequence of the host immune response. The cyst normally grows 1–5 cm in diameter annually, depending on the density of the host tissue (Carmena and Cardona, 2014; Hajizadeh et al., 2013). The cyst produces millions of protoscolices which are released when a carnivore consumes the viscera of the infected intermediate host. The swallowed protoscolices changed to adult worm that attach to the proximal small bowel to complete the life cycle (Fig. 1) (Lewall, 1998).

Fig. 1. The life cycle of *E. granulosus* the causative agent of cystic echinococcosis. A: Dogs and other canidae are the most common definitive hosts. B: The adult worm of *E. granulosus* (3–6 mm) resides in small intestine of the definitive hosts. The eggs are released from gravid proglottids and passed in the feces (infective stage for intermediate hosts). C: Intermediate host including: sheep, goat, swine, cattle and horses. Humans can become infected accidentally as intermediate hosts and harbor cysts. D: Cystic echinococcosis is localized in the liver, lungs and other organs in the body (such as the spleen, brain, heart, and kidneys). The cyst contains protoscolices, brood capsules and daughter cysts. Finally canidae are infected by ingestion of cyst which contains protoscolices that turns into adult worm.

3. Epidemiology

E. granulosus exists as a complex of diverse strains that differ in a wide variety. Molecular population genetics and phylogenetic analysis mostly based on mitochondrial DNA (mt DNA). It has been shown that *E. granulosus* comprises 10 genotypes (G1 to G10) and G1 (sheep strain) with worldwide distribution is the most important strain associated with the human CE. The other strains appear to be genetically distinct, suggesting that *E. granulosus* taxon is paraphyletic and may require taxonomic revision (Spotin et al., 2016; Sarvi et al., 2014; Moro and Schantz, 2009). The disease has also been previously recorded from most of the countries throughout the world (Rahimi et al., 2016; Eckert et al., 2001). Epidemiological studies that were carried out in Kenya, Libya and Uganda showed high canine echinococcosis prevalence (26–66%) and mean intensity of infection rates was 540–1064 worms (Inangolet et al., 2010; Buishi et al., 2006; Buishi et al., 2005). Currently very limited information is available from Western, Central, and Southern Africa where updated, reliable epidemiological data is greatly needed. This parasite is endemic or re-emerging in large parts of Asia including East Asian countries, the former Soviet republics of Central, North and Western China and Northeastern Siberia and Western Arctic. Although the infection is historically known to be present in many of the East Mediterranean regions, the Arab states bordering the Persian Gulf and a number of Southeast of Asian countries, either there is no up to dated, or very limited data regarding epidemiology of this important diseases available from these areas (Rakhshanpour et al., 2012; Wang et al., 2010; Sadjjadi, 2006; Torgerson et al., 2006; Rausch, 2003; Abdel-Hafez and Kamhawi, 1997; Dar and Alkarmi, 1997). In addition, *E. granulosus* is present in large areas of Europe, particularly those where the sheep-raising industry still represents an important contribution to the local economy, such as the Iberian, Balkan, and Italian peninsulas. Focuses of the disease are also known in Great Britain and the Baltic States (Dakkak, 2010; Carmena et al., 2008). The disease seems to be less prevalent in UK, Central Europe, the Baltic States and the Scandinavian countries (Carmena and Cardona, 2013; Romig et al., 2006). It seems that the worldwide distribution of this parasite is closely related to animal husbandry. The highest occurrence rates among humans and animals happen where livestock production is considerable, large numbers of dogs and access of dogs to carcass of infected animals after uncontrolled slaughter (Gemmell and Lawson, 1986). In addition, it should be noted that biological factors and human behavioral determine the dispersion and existence of *Echinococcus* in a mentioned regions.

4. Pathogenesis

CE has been reported to present for medical care in people aged from younger than 1 year to older than 75 years and rate of infection in both sexes are fairly similar. More than 90% of cysts occur in the liver, lungs, or both of them. Symptomatic cysts have been reported occasionally (2–3%) in the kidney, spleen, peritoneal cavity, skin and muscles; and rarely in heart, brain, vertebral column, and ovaries (1% or less) (McManus et al., 2003). The presenting features of CE rely on the organ involved, size of the cysts and their position within the organ, the mass effect inside the organ and upon adjacent structures, and complications relating to cyst rupture. Approximately 40–80% of patients with primary CE has single-organ involvement and harbor only one cyst. The mortality rate due to CE is about 2–4% and increases significantly if medical treatment is unavailable or inadequate. The most of CE cases remain asymptomatic pending the cyst compresses or ruptures and spills its contents into adjacent tissues and organs, by which time the disease is already well advanced (Larrieu et al., 2000). Hepatic cysts can cause pain in the upper abdominal region, hepatomegaly, cholestasis, biliary cirrhosis, portal hypertension, ascites, and a variety of other appearances. Cysts may rupture into the peritoneal cavity, causing anaphylaxis or secondary CE, or into the biliary tree, leading to cholangitis and cholestasis. Abscess formation is possible subsequent bacterial infection of cysts. Chronic cough, expectoration, dyspnea, hemoptysis, pleuritis, and lung abscess are selected symptoms caused by pulmonary cysts, and neurological disorders can be induced by cysts in the brain (Mandal and Deb Mandal, 2012; Nunnari et al., 2012; Larrieu et al., 2000).

5. Diagnosis

When infection is asymptomatic, methods for screening populations at high risk are inexpensive and quite easy for large-scale. Physical imaging methods, such as radiology, ultrasonography, computed axial tomography (CT scanning), and magnetic resonance imaging (MRI), are definitive diagnosis of CE (Pawłowski et al., 2001). Immunodiagnosis is another way for diagnosis of the infection. It is also useful for follow-up of patients after surgical or pharmacological treatment. One of the usual source of antigenic material for immunodiagnosis is hydatid cyst fluid antigens (Gottstein, 1992). The lipoproteins such as antigen B and antigen 5, the predominant components of hydatid cyst fluid, are extensively used in examine for immunodiagnosis of CE (Poretti et al., 1999). Some of major problems in immunodiagnosis tests are cross-reactivity with antigens of other parasites and lack of enough sensitivity and specificity. There are other methods that differences among in both specificity and sensitivity. In routine laboratory application, insensitive and nonspecific tests, such as the Cassoni intradermal test, the complement fixation test, the indirect haemagglutination test (IHA), and the latex agglutination test (LAT), have been replaced by enzyme-linked immunosorbent assay (ELISA), in-direct immunofluorescence antibody test (IFA), immunoelectrophoresis (IEP), and immunoblotting (IB) (Lightowlers et al., 1995; Babba et al., 1994). Generally, serology of CE may be advanced by integrating several defined antigens such as synthetic peptides, also the design of new *E. granulosus*-specific peptides which reacts with other false-negative sera (Babba et al., 1994).

6. Treatment

Treatment indications are multifaceted and are based on cyst features, available medical/surgical skills and equipments, and adherence of patients to long-term monitoring. The current methods for treatment of human CE include surgery (consisting of conservative and laparoscopic), and percutaneous drainage (consisting of puncture, aspiration, injection and re-aspiration; PAIR); these methods are mostly helpful for liver cysts (Brunetti et al., 2010; Smego and Sebanego, 2005). Surgery is always accompanied by chemotherapy to decrease the risk of recurrence of CE (Nunnari et al., 2012). In patients that surgery is inadequate; chemotherapy is the treatment of choice. Benzimidazole is available agent for treatment of human hydatidosis. Most studies showed that the usefulness of albendazole as measured by the disappearance of a cyst is generally less than 30% under ideal conditions. Altogether, 60% of cysts showed some response in the course of therapy, including reduction in size or detachment of cyst components from the wall (Moazeni and Mohseni, 2012b). Besides, adverse side effects have been observed with both benzimidazole, including abnormalities in liver function, leucopoenia and alopecia, and albendazole that has been shown to be teratogenic in rats and rabbits (Naseri et al., 2016; Maggiore et al., 2012; Walker et al., 2004a). With respect to these difficulties, the innovation of novel therapeutic drugs for CE treatment seems to be necessary.

7. Plant remedies in the management of hydatidosis

Newly, herbal medicines have gradually been used to treat many diseases. At the present time, many drugs originate from herbal sources and most of the effective drugs were plant-based (Jazani et al., 2009). In the current survey, we have selected several studies performed *in vitro* and/or *in vivo* scolicidal effects of herbal extracts. A systematic literature search was performed between 1996 and 2015 in PubMed, Science Direct, Scopus, and Google Scholar databases. Keywords include: "scolicidal effects"; "herbal extracts"; "protoscolices"; "hydatid cysts"; "metacestodes"; "*E. granulosus*"; "herbal medicine"; "anti-hydatid" and "biogenic particles". Table 1 shows the efficacy of studied herbal extracts against protoscolices of hydatid cyst.

Since the spillage of the cyst insides is a main cause of recurrence, inactivation of the protoscolices is strongly recommended with a scolicidal agent prior to opening or removing a cyst. Scolicidal agents used through hydatid cyst surgery are vital for surgical success owing to reduction in the risk of spillage of viable protoscolices. An ideal scolicidal agent is defined as being effective in low concentrations and exposure time, stable in cyst fluid, not affected by dilution with the cyst fluid, eliminator of cyst protoscolices, non-toxic, low viscosity, and easily available, prepared and inexpensive (Besim et al., 1998). To date, many scolicidal agents have been used for inactivation of the hydatid cyst contents, but there is no ideal agent that is effective and safe enough. Among the numerous scolicidal agents encouraged in the past, formalin was the first and most commonly used agent. In spite of its usefulness, it is no longer used because of the related toxicity and severe hepatobiliary problems (Besim et al., 1998). Severe hepatobiliary complications have been also reported for ethyl alcohol which has considerable efficacy against protoscolices (Yetim et al., 2005; LeVeen et al., 1993). No scolicidal effect can be shown with a concentration of less than 10% saline at exposure time of 5 min. The least concentration of saline should be 20% but severe hepatobiliary problems have been reported for 10–20% Nacl (Besim et al., 1998). H_2O_2 has been found to be considerably effective (90.3%) against protoscolices, while because of the side effects, nowadays it is not used in many fields (Adas et al., 2009). Developing novel and effective medication is tremendously important in today's conditions, where species are becoming resistant. Therefore, there is resurgence in the use of natural alternative therapies, instead of synthetic drugs that often have severe side effects (Haghani et al., 2014). Information from previous studies has shown that the natural products contain a large variety of substances that possess antimicrobial activity (Mahesh and Satish, 2008). With this concept, a large number of medicinal plants having their ethanobotanical history as anthelmintic are used to screen for their scolicidal potential particularly against *E. granulosus*. A number of studies describe the inhibitory effects of different natural products and their volatile components against *E. granulosus* protoscolices (Tables 1 and 2). In the following, some of important herbal extracts with high scolicidal effects were discussed.

Allium sativum: *A. sativum* (garlic) is one of the most widely investigated medical plants. *A. sativum*, a member of Liliaceae family has been reported as the source of some antihelminthic ingredients (Soffar and Mokhtar, 1991). Moazeni *et al. (*2010) investigated the efficacy of methanolic extract of *A. sativum* on scolices of hydatid cyst and indicated a high scolicidal activity of methanolic extract *in vitro,* as concentration of 25 mg/mL at 60 min eliminated 100% of protoscolices. Moreover, the scolicidal activity of *A. sativum* extract at the concentration of 50 mg/mL was 100% after 10 min of application. In other study that were conducted among hazelnut, squash seeds and garlic chloroformic and hydro-alcoholic extracts, garlic had more potent scolicidal effects among all the three plants and killed 98% of protoscolices in 50 mg/mL at 20 min (Eskandarian, 2012). Sadjjadi et al. (2008) used different *A. Sativum* extracts and the results showed that chloroformic extract of the

Table 1
Natural herbal extracts used against protoscolices of hydatid cyst both *in vitro* and *in vivo*.

Scientific name	Part used	Concentration/Dose	Extract	Type of study	Main outcome	Ref.
Mallotusphilippinensis	Fruits	10 and 20 mg/mL	Methanolic	*In vitro*	High scolicidal activity (100%) at concentration of 20 mg/mL after 2 h. As compared with the standard drug praziquantel, *M. philippinensis* extract had significant scolicidal activity	Gangwar et al. (2013)
Saturejakhuzistanicab (Jamzad)	Aerial parts	3, 5 and 10 mg/mL	Essential oil	*In vitro*	High scolicidal activity (100%) at concentration of 10 mg/mL after 10 min	Moazeni et al. (2012a)
Trachyspermumammi L (Ajowan)	Fruits	3, 5 and 10 mg/mL	Essential oil	*In vitro*	Significant scolicidal activity (100%) at concentration of 10 mg/mL after 10 min	Moazeni et al. (2012b)
Sambucusebulus	Fruits	1,10, 50 and100 mg/mL	Methanolic	*In vitro*	Scolicidal effect of any concentrations of ethanolic extract of *S. ebulus* was extremely significant. Scolicidal activity at concentration of 100 mg/mL after 60 min was 98.6%	Gholami et al. (2013)
Coriandrumsativum	Seeds	0.25, 0.5, 0.60.75 mg/mL	Phenolic	*In vitro*	High scolicidal activity (100%) at concentration of 0.75 gm/mL after three days	Al-Maliki (2008)
Oleaeuropaea	Leaves	0.1, 0.01, 0.001%	Aqueous	*In vitro*	96.7% of protoscolices lost viability at concentration of 0.01% at 120 min	Zibaei et al. (2012)
S. khuzestanica	Leaves	0.1, 0.01, 0.001%	Hydro alcoholic	*In vitro*	All of the protoscolices died in 0.1% concentrations after 120 min	Zibaei et al. (2012)
Trametesrobiniophilamurr (Huaier)	Leaves	0, 0.5, 1, 1.5, 2, and 2.5 mg/mL	Aqueous	*In vitro/ In vivo*	*In vitro*huaieraqueous extract showed low protoscolicidal activity and after 24 days 50% of protoscolices were viable *In vivo treatment was effective and 75% of mice were not infected*	Lv et al. (2013)
Mentha. pulegium	Leaves	10,5, and 1 μg/mL	Essential oils	*In vitro*	The highest protoscolicidal activity was observed at concentration of 10 μg/mL after 12 days of incubation	Maggiore et al. (2012)
M. piperita	Leaves	10,5, and 1 μg/mL	Essential oils	*In vitro*	The viability of protoscolices decreased to approximately 50% at concentration of 10 μg/mL after 24 days	Maggiore et al. (2012)
Zingiberofficinale R	Rhizomes	25, 50 and 100 mg/mL	Methanolic	*In vitro*	High scolicidal activity at concentration of 100 mg/mL after 30 min	Moazeni and Nazer (2011)
*Corylus*spp.(Squash)	Seed	50 mg/mL	Hydro alcoholic, chloroformic and mixture of both extracts	*In situ*	Chloroformic extract killed 36% of protoscolices in 50 mg/mL at 60 min	Eskandarian (2012)
*Curcurbia*spp.(Hazel)	Nut	50 mg/mL	Hydro alcoholic, chloroformic and mixture of both extracts	*In situ*	Chloroformic extract killed 47% of protoscolices in 50 mg/mL at 60 min	Eskandarian (2012)
A. sativum (Garlic)	Cloves	50 mg/mL	Hydro alcoholic, chloroformic and mixture of both extracts	*In situ*	Chloroformic extract of garlic had the most potent protoscolicidal activity and killed 98% of protoscolices in 50 mg/mL at 60 min	Eskandarian (2012)

Table 1 (*Continued*)

Scientific name	Part used	Concentration/Dose	Extract	Type of study	Main outcome	Ref.
Peganumharmala	Seeds	250, 125, 62.5, 31.25, 15.6, 7.81, 3.91) mg/mL	Ethanolic and crude alkaloids	*In vitro*	Crude alkaloid extract was more effective than the ethanolic extract and protoscolices mortality rate was 100% at concentration of 250 mg/mL after 24 h	Hammoshi et al. (2005)
Capparisspinosa	Leaves and seeds	5, 10, 20 mg/mL	Ethanolic and hexane	*In vitro*	90-100% mortality rate of protoscolices with both extract in all of concentrations after 120 min	Al-Barwary (2014)
Dendrosicyossocotrana	Leaf	1000, 2000 and 5000 μg/mL	Aqueous and methanolic extracts	*In vitro/ in vivo*	*In vitro* the highest (100%) protoscolicidal activity was observed at concentrations of 5000 μg/mL usingmethanolic extract after 360 h. *In vivo* study also showednoticeable inhibitory effects.	Barzinji et al. (2009)
Jatrophaunicostata	Leaf	500, 750 and 1000 μg/mL	Aqueous and methanolic extracts	*In vitro/ in vivo*	*In vitro* the highest (100%) protoscolicidal activity was seen at concentrations of 1000 μg/mL using methanolic extract after 288 h. *In vivo* study also showednoticeable inhibitory effects.	Barzinji et al. (2009)
Hymenocarterlongiflorus	Leaves, stems and inflorescences	50, 100, 150, 200, 250 μg/mL	Essential oil and methanolic	*In vitro*	Essential oil and the methanolic extract exhibited significant toxic activity against the larvae of *E. granulosus* with LC50 values of 79.6 and 135.8 μg/mL	Taran et al. (2013)
A. sativum	Cloves	500 mg/mL (aqueous extract and hydro-alcoholic extract), 100 and 200 mg/mL of chloroform extract	Aqueous, chloroform hydro-alcoholic and simple extract	*In vitro*	Chloroformic extract of garlic with 200 mg/mL concentration had the highest protoscolicidal activity after 60 min	Sadjjadi et al. (2008)
Zatariamultiflora	Leaves	10 and 25 mg/mL	Methanolic	*In vitro*	Scolicidal effect at a concentration of 25 mg/mL was 100% after 1 min	Moazeni and Roozitalab (2012)
Z. multiflora	Leaves	0.12%(wt/v)	Aromatic water	*In vitro*	Protoscolices mortality rate was 100% after 5 min	Moazeni et al. (2014b)
Z. multiflora	Leaves	2.5, 5, 10, 20 mg/mL	Methanolic	*In vitro*	Z. multiflora extract at the concentration of 20 mg/mL after 10 min of exposure eliminated 100% of protoscolices	Jahanbakhsh et al. (2016)
Z. multiflora	Leaves	1, 10, 15, 17.5, 20, 25, 50, 75 and 100 μg/mL	Essential oils	*In vitro*	All of the protoscolices killed in 17.5 μg/mL concentration after 10 min	Kavoosi and Purfard (2013)
Ferula assafoetida	Leaves	1, 10, 25, 50, 60, 70 and 80 μg/mL	Essential oils	*In vitro*	All of the protoscolices eliminated in 60 μg/mL concentration after 10 min	Kavoosi and Purfard (2013)
Ocimumbacilicum	Leaves	25, 50 and 100 mg/mL	Methanolic	*In vitro*	Low scolicidal activity and 50 mg/mL concentration of extract after 60 min, killed only 24.1% of protoscolices	Haghani et al. (2014)
Allium cepa	Root	25, 50 and 100 mg/mL	Methanolic	*In vitro*	Low scolicidal activity was seen. Concentration of 100 mg/mL after 60 min eliminated 16.8% of protoscolices	Haghani et al. (2014)
Berberis vulgaris (Barberry)	Fruits	0.5, 1, 2 and 4 mg/mL	Aqueous	*In vitro*	The highest effect was observed in 4 mg/mL and 5 min	Rouhani et al. (2013)

Table 1 (*Continued*)

Scientific name	Part used	Concentration/Dose	Extract	Type of study	Main outcome	Ref.
Berberis vulgaris	Root	*Berberis*:0.25, 0.5, 1 and 2 mg/mL	Methanolic	*In vitro*	100% inhibition effect against protoscolicesat the concentration of 2 mg/mL after 10 min	Mahmoudvand et al. (2014b)
Berberine	Root	*Berberine*: 0.062, 0.125, 0.25 and 0.5 mg/mL	Main Compound of *B. vulgaris*	*In vitro*	100% fatality rate against protoscolices at the concentration of 0.5 mg/mL after 10 min incubation	Mahmoudvand et al. (2014b)
Rhuscoriaria L.	Fruits	10, 30 and 50 mg/mL	Methanolic	*In vitro*	Concentration of 50 mg/mL after 10 min had high protoscolicidal activity	Moazeni and Mohseni (2012a)
Nigella Sativa	Seeds	12 and 25 mg/mL for one week (oral route)	Aqueous	*In vivo*	High efficiency was observed with all concentrations especially with 25 mg/mL concentration Degeneration and necrosis of the cyst wall and less number of cysts inmice treated with 25 mg/mLconcentration	Al-Mayah et al. (2012)
Salvia officinalis(Salvia)	Aerial parts	2500, 1500, 1000, and 500 μg/mL	Alcoholic	*In vitro*	Complete loss of viability of protoscolices occurred with 500 μg/mL concentration of extract at day 6 post-treatment	Yones et al. (2011)
Thymus vulgaris (Thyme)	Aerial parts	2500, 1500, 1000, and 500 μg/mL		*In vitro*	Complete loss of viability of protoscolices occurred with 500 μg/mL concentration of extract at day 7 post-treatment	Yones et al. (2011)
Z. multiflora	Leaves	Preventive trial: 4 g/L for 8 months. Therapeutic trial 8 g/L of extract for 30 days (oral route)	Methanolic	*In vivo*	In preventive trial, hydatid cysts developed in only one mouse out of 10 animals (10%) In therapeutic trial, hydatid cysts developed in four mice out of five animals	Moazeni et al. (2014a)
Z. multiflora		Preventive effect:20 mL/liter in drinking water for 8 months Therapeutic effect:40 mL/liter in drinking water for 30 days	essential oil from aromatic water		In preventive effect: no hydatid cyst development occurred in mice treated with *Z. multiflora* The therapeutic effect of *Z. multiflora* on hydatid cysts was almost comparable to that of albendazole	Moazeni et al. (2014c)
PeganumHarmala L (Harmel)	Seeds	25%, 50%, 75% and 100%	Aquatic	*In vitro*	Very low scolicidal activity, 4.5% protoscolicidal activity after 60 min	Nematollahi and Ghazi (2014)
Menthapiperita,		1, 5 and 10 μg/mL	Essential oils	*In vitro*	10 μg/mL of essential oil caused a reduction in the viability of 77, 82, and 71% of protoscolicesat day 7	Albani et al. (2014)
Menthapulegium		1, 5 and 10 μg/mL	Essential oil	*In vitro*	10 μg/mL of essential oil lead to decrease in the viability of 82% of protoscolicesat day 7	Albani et al. (2014)
Rosmarinusofficinalis		1, 5 and 10 μg/mL	Essential oil	*In vitro*	10 μg/mL of essential oil produced a reduction in the viability of 71% of protoscolicesat day 7	Albani et al. (2014)
Pistaciakhinjuk	Leaves	128, 256, 512 μg/mL	Ethyl alcohol, Chloroform, Ethyl acetate and essential oil	*In vitro*	Moderate anthelmintic activity. Only essential oil inducedsignificant decrease in viability of protoscolices after 48 h with concentrationof 512 μg/mL	Taran et al. (2009)
Nigella sativa (Black cumin)	Seeds	0.1, 0.01, 1 and 10 mg/mL	Essential oil	*In vitro*	Potent scolicidal activity at the concentration of 10 mg/mL after 10 min	Mahmoudvand et al. (2014a)

Table 1 (*Continued*)

Scientific name	Part used	Concentration/Dose	Extract	Type of study	Main outcome	Ref.
Peganumharmala L.	Seeds	50–4000 mg/mL	Aquatic and alcoholic	*In vitro*	Alcoholic extract had significant protoscolicidal effect and scolicidal effect at a concentration of 4000 mg/mL was 100% after 30 min	Ma et al. (2007)
A. sativum	Cloves	50 mg/kg body weight/mouse	Aqueous	*In vivo*	Efficient as prophylactic and therapeutic agent, significant enhancing effects on the immune system	Ali et al. (2016)
A. sativum	Cloves	25 and 50 mg/mL	Methanolic	*In vitro*	High scolicidalactivity.Scolicidal activity at the concentration of 50 mg/mLwas 100% after 10 min of application	Moazeni and Nazer (2010)
Sophoramoorcroftiana	Seeds	0.75, 1.50, 3, 6, g/L	Alkaloids	*In vitro/In vivo*	100% scolicidal activity when alkaloids were given at 6 g/L for 7 days Alkaloids alone at the dose of 50 mg/kg/day significantly decreased the hydatid cyst weights compared with untreated mice	Ma et al. (2007)
Stephaniatetrandra	Roots	N/A	Alkaloid	*In vitro/In vivo*	Obvious killing effect on the protoscolices	Bao et al. (2003)
Foeniculumvulgare	Seeds	0.125, 0.25, 0.5 and 1 mg/mL	Essential oil	*In vitro*	*F. vulgare* essential oil at concentration of 1 mg/mL killed 100% protoscolices after 5 min of exposure	Lashkarizadeh et al. (2015)

Table 2
Other natural extracts used against protoscolices of hydatid cyst.

Natural product	Concentration/Dose	Type of study	Main effect	Ref
Vinegar	1, 5, 10, 15, 20, 25, 50 and 100% v/v	*In vitro*	Scolicidal activity was 100% in the concentration of 50%	Hajihossein et al. (2015)
Honey	1, 5, 10, 25, and 50%	*In vitro*	Highly effective at concentration of 10%	Kilicoglu et al. (2006)
Aspergillusniger	0. 015, 0. 031, 0. 0625, 0. 125, 0. 25, 0. 5, 100 mg/mL	*In vitro*	High scolicidal activity compared with albendazole at the same concentration	Hameed et al. (2010)
Cladophoracrispate	280, 300, 330, 100, 110, 120, 500 μg/mL	*In vitro/in vivo*	Positive effect on the protoscolices of hydatid cyst	Athbi et al. (2014))
Pestalotiopsis spp.	5 to 30 mg/mL	*In vitro*	Significant anticestodal activity	Verma et al. (2013)
Fungal chitosan	50, 100, 200, 400 μg/mL	*In vitro*	Satisfactory scolicidal activity	Fakhar et al. (2013)
Endophytic fungi	100 mg/mL	*In vitro*	Loss of turgidity due to leakage of cell contents	Verma et al. (2014)

plant with 200 mg/mL concentration had the highest protoscolicidal activity (99.58 ± 1.63). The protoscolicidal activity was time dependent and increased by the time of exposure. Several studies have suggested that nitric oxide (NO) plays exclusive role in the liver, and its involvement in a diversity of hepatic processes is supported by the finding that the majority of cells found in the liver (hepatocytes, Kupffer cells, fat-storing cells, and endothelial cells) are able to produce NO under passable stimulation (Brunet et al., 1999). NO is an important vascular and neuronal messenger molecule which has emerged as an important mediator of a variety of biological functions. One of the most prominent functions of NO is its participation in antimicrobial defense. Many cell types, for instance macrophages, can express high levels of iNOS when activated by immunological stimuli such as interferon gamma (IFN-γ) or tumor necrosis factor (TNF), resulting to kill parasites (Liew et al., 1997). Evaluation of the efficacy of *A. sativum* on serum NO level and hepatic histopathology in experimental CE in mice showed that *A. sativum* is effective as prophylactic and therapeutic agent in CE with the additional advantage of being a natural product. It seems that *A. sativum* might be used as a scolicidal agent in the surgical treatment of the hydatid cyst. Although A. sativum is edible, its possible side effects when used as a scolicidal agent need more investigations (Liew et al., 1997).

Zataria multiflora: *Z. multiflora* is one the most reputable herbal medicines that belongs to the *Lamiaceae* family. The composition, antioxidant, antibacterial, antifungal, and anti-inflammation activities of the essential oil from *Z. multiflora* have been previously studied (Saei-Dehkordi et al., 2010; Zargari, 1992). Moazeni et al. (2014) indicated high scolicidal effect of methanolic extract of *Z. multiflora* on hydatid cyst. The concentrations of 10 mg/mL and 25 mg/mL killed 100% of protoscolices after 3 min and 1 min, respectively. In another study, Kavoosi *et al.,* showed that all protoscolices were killed after 10 min of exposure time at concentrations more than 17 μg/mL of essential oil from *Z. multiflora*. It seems that the essential oil might be exerted its scolicidal activity by change membrane permeabilization. In the mitochondria, essential oils induce membrane depolarization and reduce membrane potential. Generally, the main components of *Zataria* oil are phenolic monoterpenes, carvacrol, and thymol. Study on the antimicrobial activity of monoterpenes indicated that the extent of antibacterial activity persuaded by monoterpenes but the scolicidal mechanisms of monoterpenes has not been presently recognized; however, this scolicidal effect might be applied by apoptosis induction (Kavoosi and Purfard, 2013). *In vivo* study of effects of *Z. multiflora* methanolic extract on hydatid cyst showed that *Z. multiflora* is not only effective in the prevention of hydatid cyst formation and development, but also is effective in the treatment of hydatidosis in infected mice. Results of the study indicated that the concentration 4 g/L in drinking water for 8 months prevented formation and development of the hydatid cyst in laboratory mice and this preventive effect was comparable with the preventive effect of albendazole (150 mg/kg BW/day for 10 days). Furthermore, concentration of 8 g/L in drinking water for 30 days has therapeutic effect on the hydatid cyst (Moazeni et al., 2014a). High-performance liquid chromatography)HPLC(analysis of phenolic compounds of *Z. multiflora* extract showed that gallic acid, catechin, caffeic acid, and quercetin are as major phenolic compounds (Jahanbakhsh et al.; Moazeni et al., 2014a; Moazeni et al., 2014b; Moazeni et al., 2014c; Saei-Dehkordi et al., 2010). More studies are required to identify the precise mechanisms of scolicidal activity of phenolic monoterpenes.

Mentha* spp.:* The genus *Mentha L. (Lamiaceae)* comprises more than 25 species, mainly perennial herbs growing wildly in damp or wet places throughout temperate regions of Eurasia, Australia, and South Africa (Gulluce et al., 2007; Pexoto et al., 2010). Study of anthelminthic of efficacy of *M. piperita* and *M. pulegium* essential oils on *E. granulosus* protoscolieces and metacestodes by Marina *et al.,* showed *M. pulegium* had a significantly stronger effect than *M. piperita*. Maximum protoscolicidal effect at 10 μg/mL concentration of *M. pulegium* was observed after 12 days of incubation (9.3% ± 2.6%) and reached 0% after 18 days. *M. pulegium* at concentrations of 1 and 5 μg/mL provoked a later effect; reducing viability to 0% between 24 and 18 days (Maggiore et al., 2012). The observed differences of the efficacy of the essential oils of *M. pulegium* and *M. piperita* could be explained by the differences of their elements. Gas chromatography–mass spectrometry (GC–MS) investigation showed piperitone oxide is the main compound of *M. pulegium* and this component could be the responsible of the markedly detected anthelmintic effect (Pexoto et al., 2010) Generally, results of study pointed a promising source of potential protoscolicidal agent. However further bioassays *in vitro* and *in vivo* are required to fully assess the potential effect of these essential oils as valuable anthelmintics for the treatment of CE.

Nigella sativa: *N. sativa L.* (*Ranunculaceae* family) is usually known as black seed grown in the Middle East, Eastern Europe, and Western and Middle Asia which is traditionally used as a natural treatment for a number of diseases (Ali and Blunden, 2003). Mahmoudvand *et al. (*2014) indicated that the essential oil of *N. sativa* at the concentration of 10 mg/mL after 10 min of exposure time eliminated 100% of protoscolices. Similarly, the mean mortality rate of protoscolices after 20 min of exposure to the concentration of 1 mg/mL was 100%. GC/MS investigation showed thymoquinone (42.4%) as main ingredient of the *N. sativa*. Moreover, it has previously been proven that thymoquinone administrated at the concentrations of 0.01, 0.02, and 0.03% for 90 days had no mortality and signs of toxicity in the drinking water for mice (Badary et al., 1998). Generally, the findings of study indicated a high scolicidal activity of *N. sativa* essential oil and its potential as a natural source for synthesis of a new scolicidal agent for application in hydatid cyst surgery.

Berberis vulgaris: *B. vulgaris* known with different names, mostly with the common name of barberry, has a long history of being a therapeutic medicine (Aryane et al., 2007). *Barberry* and its related components inhibit the growth of many microorganisms including fungi, protozoa, and bacteria *in vitro* (Amin et al., 1969). Rouhani et al. (2013) in a study on the scolicidal effect of *barberry* with different concentrations (0.5, 1, 2, and 4 mg/mL diluted form) and at different exposure times (5, 15, and 30 min) observed that in 4 mg/mL dilution with the mean of scolicidal activity had 100% efficacy after 5 min *B.vulgaris* extract at the concentration of 2 mg/mL killed 96, 98, and 98.7% of protoscolieces after 5, 15, and 30 min of application, respectively. The results of survey showed that *B. vulgaris* has a high scolicidal activity *in vitro*; also it was completely effective in low concentration (4 mg/mL) and short exposure time (5 min). So, this natural component can be used as a potent alternative scolicidal agent in surgery (Rouhani et al., 2013).

Trachyspermum ammi L* (ajowan)*: Ajowan belongs to the family of *Apiaceae* and is known as a popular aromatic herb and spice which grows in India, Iran, and Egypt. Ajowan has been known to possess anthelmintic activities (Lateef et al., 2006; Pandey et al., 2009). In addition, *in vitro* effect of ajowan essential oil on hydatid cyst protoscolieces proved a high scolicidal activity. Ajowan essential oil at the concentration of 5 mg/mL killed 88.64 and 100% of protoscolices after 30 and 60 min, respectively. One hundred percent scolicidal effect was observed with ajowan essential oil at the concentration of 10 mg/mL after 10 min of application. GC–MS analysis reported that thymol (50.07%), γ-terpinene (23.92%), and *p*-cymene (22.9%) are as major essential oil constituent. Among them thymol has been reported to have anthelmintic activity (Moazeni et al., 2012b). Thymol exerts its anthelmintics activity by interference with the energy metabolism of parasites through potentiation of ATPase activity and result in loss of energy reserves (Lateef et al., 2006). Though terpinene was the second main constituent identified in the ajowan oil, no strong antibacterial activity had been reported from its gamma isomer. Also *p*-Cymene is another major compound identified in ajowan oil that is not an effective antimicrobial agent when used alone (Burt, 2004). Several studies have displayed that the whole essential oil has a stronger antiseptic activity than the individual major components, representing that the minor constituents are also important to the antimicrobial activity and might have a synergistic influence (Burt, 2004; Gill et al., 2002). Safety of the herb oil for pharmaceutical purposes as a novel scolicidal agent and *in vivo* efficacy of the ajowan essential oil also requires to be determined using an animal model of hydatid cyst infection.

***Satureja khuzistanica* (jamzad):** This plant belongs to the *Lamiaceae* family and has some medical uses like antifungal and antimicrobial properties. *In vitro* scolicidal effect of *S. khuzistanica* essential oil indicated that at the concentration of 5 and 10 mg/mL, 81 and 100%, of protoscolices were killed, respectively. Result of the study exhibited both dose-dependent and time-dependent scolicidal effect of this plant (Moazeni et al., 2012a).

8. Nanoparticle synthesis from plant extracts

Nanoparticles (NPs) due to their large surface-volume ratio have been showed several exclusive properties. NPs are also able to enter cells more often than other particles (Ingale and Chaudhari, 2013). Synthesized green NPs of biological sources like plants are widely accomplished, because they are less toxic to human compared with other chemical medicines. Mahmoudvand et al. (2014) conducted a study on effects of biogenic selenium NPs against protoscolices of hydatid cysts. The results showed potent scolicidal effects at concentrations of 250 and 500 and mg/mL after 10 and 20 min of application (Mahmoudvand et al., 2014c). Rahimi et al. (2015) showed that green syntheses of Ag-NPs have an effective and promising scolicidal activity. The result of study indicated that the concentrations of 0.1 and 0.15 mg/mL after 120 min of exposure time had 83% and 90% mortality rate, respectively.

Plant extracts contain different constitutes like polysaccharides, antioxidant metabolites, phenolic compounds and flavonoids which are used as a rapid, easy and clean process for herbal preparation of metallic nanoparticles (Liang et al., 2010; Ponarulselvam et al., 2012; Satyavani et al., 2011). The main point is that the herbal-mediated process for biosynthesis of metallic nanoparticles does not change the nature of metallic nanoparticles to natural products. The bioactive constitutes in the plant extract, alter the metallic ions to nano-metals in a safe and eco-friendly method and play a surfactant role for extremely high stability of nanoparticles (Abdelmonem and Amin, 2014) also maybe interfere in the anti-parasitic activity of metallic nanoparticles, but in spite of all mentioned facts, herbal-mediated preparation of metallic nanoparticles only accepted as a green process and does not affect the nature of nanoparticles.

9. Future directions

Herbal medicines are now in great request in the developing world for primary health, upkeep not only they are inexpensive but also for better cultural acceptability, compatibility with the human body and their negligible side effects. Medicinal herbs as possible source of therapeutics helps has achieved an important role in health system all over the world for both humans and animals not only in the disease but also as potential material for maintaining proper health. A major factor obstructing the development of the medicinal plant based on industries in developing countries has been the lack of information on the social and economic welfares that could be derived from the industrial use of medicinal plants. Though there is substantial published ethanobotanical information regarding treatments, especially for helminths, there are few published investigations about active components in the scientific literatures. A number of compounds from plant sources have been shown to have certain scolicidal activity in laboratory trials include *A. sativum*, *Z. multiflora*, *M. pulegium*, *N. sativa*, *B. vulgaris*, *T. ammi L* and *S. khuzistanica*. As a first step in developing new drugs, there is a crucial need for considerable funding to let the complete evaluation of medicinal plant products as potential scolicidal agents. The World Health Organization (WHO) lately convened a Scientific Working Group worried with traditional medicine and pharmaceutical medicine viewpoints on natural products recognizing the importance of natural products for the treatment of tropical diseases. Considering the limited diversity of scolicidal agents, development of new scolicidal compounds, particularly from natural sources, is of great attention. Therefore, evaluation and replacement of some new agents particularly from herbal extracts are highly recommended to combat the challenges of CE.

Conflict of interest

The authors declare that they have no conflict of interest associated with this study.

Uncited reference

Mahdavi and Masoud (2001).

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