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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 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

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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).

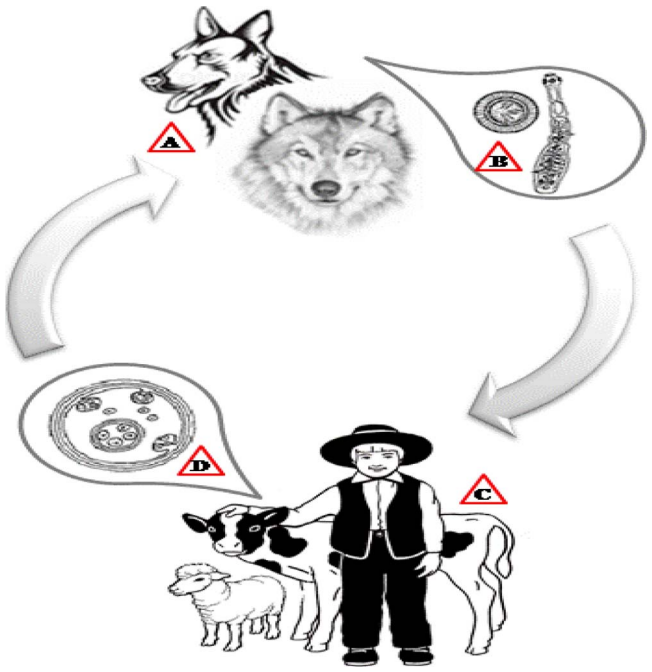

Fig. 1. The life cycle of *E. granulosus* the causative agent of cystic echinococcosis. A: Dogs and other canidae are the most common definitive hosts. B: The adult worm of *E. granulosus* (3–6 mm) resides in small intestine of the definitive hosts. The eggs are released from gravid proglottids and passed 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., 2017; 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,