Review Article

Scolicidal Effect of Some Herbs on *Echinococcus granulosus* Protoscoleces: a Systematic Literature Review

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Abstract

Surgery is the best choice of treatment for human hydatidosis. Secondary infection is one of the end points of surgery in treating the hydatidosis which results from the spillage of protoscolices into the peritoneal cavity. Many chemical scolicidal agents have been used for inactivation of the cyst's content, but most of them are associated with adverse side effects. Some studies have reported that traditional plants might have a potential application in prevention of post-surgery infections. We searched Medline, PubMed and Google scholar to identify the potentially relevant studies on implication of traditional plants against *Echinococcus granulosus* protoscoleces. In this study, we have reviewed scolicidal effects of some plant species (such as *Zataria multiflora*, *Berberis vulgaris*, *Allium* spp. *Mentha* spp. and etc.) and their products (essential oils, methanolic extract, aqueous extract and etc.) on *Echinococcus granulosus* protoccoleces. The scolicidal activity of these herbs could be helpful in hydatid cyst surgery. However, the mechanisms by which plant extracts killed protoscolices and also their safety for human cells are unclear and needed to be more investigated.

Keywords: Herbs, Scolicidal effect, Hydatidosis, Surgery

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Introduction

Human hydatidosis is a zoonotic infection caused by the larval stages of *Echinococcus granulosus* (taeniid tapeworm). Hydatidosis is recognized by long-term growth of hydatid cysts in the different organs (liver, spleen, lung, muscle, brain and etc.) of human and other intermediate hosts (1). Hydatidosis still remains a major public health problem in many parts of the world with pastoral communities, especially in regions of South America, East Africa, Eastern Europe, Russia, the Mediterranean littoral and Middle East, Central Asia and China (2). Treatment depends on stage, size, localization and complications of the cysts (3). Currently, four treatment modalities are in use for hydatid disease: chemotherapy, percutaneous aspiration, injection and reaspiration (PAIR) and surgery (4). Chemotherapy with benzimidazoles such

as albendazole and mebendazole, broad-spectrum anthelmintics, is not an ideal treatment and 20–40% of cases do not respond favorably to these drugs (5). Moreover, it has shown different adverse side effects with both benzimidazoles, such as nausea, vomiting, eosinophilia, dizziness, mild abdominal pain, leucopoenia, alopecia, pruritis, rash and headaches (6). PAIR is a percutaneous treatment method for hydatid disease. This method is invasive and should only be performed in highly specialized centers with appropriately trained and experienced staff (4).

Surgery remains as the best choice of treatment for human hydatidosis (3, 4). However whilst operating, prevention of leakage or spillage of protoscolices into the peritoneal cavity and wound edges is very important (7). Spillage of a protoscolices can cause recurrence or secondary infection that occurs in approximately 10% (8.5–22.0%) of the postoperative cases (8). In addition, it can cause anaphylactic shock that is a life-treating situation in hydatidosis surgery (9). Therefore, the use of a scolicidal agent with high effectiveness and low side effect is necessary during and after surgery.

This literature review aims to provide an overview of the efficacy of plant medicines that were developed and used for inactivation of the cyst content intraoperative. This paper presents the first critical review of literature on the use of plant medicines in surgery of the hydatidosis. The review begins with an introduction about the importance of plants and their products on hydatid cyst surgery and then an outline of the search strategy. Next in results and discussion, we provide an overview of the plants characteristics and a summary of their impact against *Echinococcus granulosus* protoscoleces.

Materials and Methods

A search of relevant literature published from 2000 to 2015 was undertaken on Medline, PubMed and Google scholar using the key words herbs, herbal medicines, plant extract and therapeutic effects, hydatid surgery, hydatidosis, scolicidal effect, and protoscoleces. Articles that were written in English and relevant to the topic were recorded in this study. Additional citations were identified by reviewing reference lists of pertinent articles. We excluded studies which had not control group and also those with minimal importance on the topics and methodological weakness. Finally, a total of 18 articles were reviewed. Pre-designed data extraction forms were used to collect data. All papers were reviewed by two reviewers (A.R. and M.T) independently for detailed evaluation. When the two reviewers were unable to reach an agreement, the third one (S.F) was included in the decision.

Results and Discussion

Ajowan (Trachyspermum ammi L.)

Trachyspermum ammi belonging to family Apiaceae and is cultivated in Egypt, Iraq, Iran, Afghanistan, Pakistan, and India (10). Moazeni *et al*. have demonstrated that ajowan essential oil (EO) had a high scolicidal activity against *E. granulosus* protoscoleces (11). Their results showed that ajowan EO had 100% scolicidal effect on the concentration of 5 and 10 mg/mL after 60 and 10 minutes, respectively. This result demonstrated that scolicidal activity of ajowan EO is comparable with scolicidal power of 20% silver nitrate (20min), 95% ethyl alcohol (15min), 20% hypertonic saline (15min) and 0.5–1% cetrimide (10 min) (11). It is assumed that thymol, main oil component of ajowan, is responsible for scolicidal activity of ajowan (11). Previous studies have shown antibacterial, antifungal and anthelmintic activity of thymol (12-15). Interference with the energy metabolism of parasites through potentiation of ATPase activity is the possible mechanism by thymol to its anthelmintics activity.

Lamiaceae (*Zataria multiflora*)

Zataria multiflora is one of the most popular herbal medicines in Iranian traditional medicine. Avishane Shirazi is the Persian name for Zataria multiflora Boiss (Z. multiflora), belonging to the family Labiatae, and it is native to Iran (16). Several previous studies indicated antifungal and antiprotozoal activity of Lamiaceae (16-20). Currently, two *in vitro* studies demonstrated high scolicidal activity of Lamiaceae (21, 22). In a study conducted by Moazeni *et al.*, *Z. multiflora* extract at a concentration of 10 mg/ml killed 68.9%, 93.7%, and 100% of protoscoleces after 1, 2, and 3 min, respectively and its scolicidal activity at a concentration of 25 mg/ml was 100% after 1 min (22). In another study Kavoosi *et al*. found that all protoscolices were killed after 10 min of exposure to

concentrations more than 0.017 mg/ml of essential oil from *Z. multiflora* (21). These studies were followed by an *in vivo* study the proved preventive and therapeutic effects of *Z. multiflora* (23). Thymol and carvacrol are the main constituents of the essential oil of *Z. multiflora* (24).

Berberis vulgaris

Berberis vulgaris, also known as European barberry, is a bush with yellow to brown coloured bark and grows in Asia and Europe. Various parts of this plant including its root, bark, leaf and fruit have been used as folk medicine for long time in Iran (25). Scolicidal activity of *B. vulgaris* was investigated by two *in vitro* studies (26, 27), suggesting high scolicidal activity of this plant. In a study by Rouhani *et al*. scolicidal effect of *B. vulgaris* with different concentrations (0.5, 1, 2, and 4 mg/ml diluted form) and at different exposure times (5, 15, and 30 min) was evaluated. Their result showed that concentrations of 4mg/ml had 100% scolicidal activity in short exposure time (5 min). Moreover, *B. vulgaris* aqueous extract at the concentration of 2 mg/ml killed 96, 98, and 98.7% of protoscoleces after 5, 15, and 30 min of application, respectively. In another study by Mahmoudvand *et al*. it has been shown that concentration of 2 mg/ml of root extract killed all of protoscoleces after 10 minutes. It has been shown that isoquinoline alkaloids such as berberine are most important constituents of this plant (28). Consistent with the above -mentioned statement, berberine at the concentration of 0.5 mg/ml killed all of protoscoleces after 10 minutes (26). Moreover, anti-parotozoal activities of B. vulgaris and berberine against Giardia lamblia, Trichomonas vaginalis, Entamoeba histolytica and Leishmania spp. have been proven (29-32).

***Allium* spp. (Garlic and onion)**

Garlic is a perennial bulb-forming plant that is popular due to its prophylactic and therapeutic activity and belongs to the family Liliaceae (33, 34). *Allium* species occur in temperate climates of the northern hemisphere. Previous studies demonstrated antibacterial, antiprotozoal and antihelminthic activity of garlic (35-41). An *in vitro* study showed that *Allium sativum* extract at the concentration of 25 and 50mg/ml killed 99.6% and 100% of the protoscolices after 50 and 10 min of application, respectively (42). In another study, Sajjadi *et al*. investigated the protoscolicidal activity of aqueous, chloroformic, and hydro-alcoholic extracts of garlic. Their results have demonstrated that 100 and 200 mg/ml concentration of garlic chloroform extract had high scolicidal activity after 4 hr and 30 min of application, respectively (43).

Allium cepa (onion) is another species of *Allium* genus which was investigated by Haghani *et al.* against hydatid cyst. A hypothesis for this survey was high scolicidal activity of garlic; however their study revealed that the scolicidal effect of this plant is not high. Their results demonstrated that the maximum concentration of onion extract (10%) killed only 16.8% of protoscolices. This result is in contrast with previous studies on *A. cepa* that showed significant antibacterial and anti-protozoal effect of *A. cepa* (44, 45).

***Mentha* spp.**

Mentha or mint is a genus of plants in the family Lamiaceae. The genus has approximately 25 species and distributed in across the world such as Europe, Africa, Asia, Australia, and North America (46). Maggiore *et al*. investigated scolicidal activity of *M. pulegium* and *M. piperita* by an *in vitro* study (47). They found that *M. pulegium* had a considerably stronger effect than *M. piperita* against protoscolices. Essential oil of *M. pulegium* produced dose- and time-dependent effects. Maximal protoscolicidal effect at this concentration was observed at concentration of 5 and 10μg/ml after 24 and 18 days of incubation (100% scolicidal activity). Whereas, 24 days after incubation, the viability of protoscoleces decreased to approximately 50% when protoscoleces were exposed to *M. piperita* (47). Previous studies have demonstrated that piperitone and isomenthol are the predominant component of *M. pulegium* and *M. piperita*, respectively (47, 48). Antibacterial effects of these components has been shown previously (49-52), however the study by Maggiore *et al*. describes for the first time the *in vitro* anthelmintic effect of *Mentha* spp.

Ginger (*Zingiber officinale*)

Zingiber officinale is a flowering plant, belonged to the family Zingiberaceae and mostly distributed in East Asia and tropical Australia. Its rhizome, root are widely used as a spice or a folk medicine (53).

Moazeni *et al*. reported that *Z. officinale* produced dose- and time-dependent effects against protoscolices of *E. granulosus*. Their results showed that scolicidal activity of *Z. officinale* extract at concentration of 25, 50 and 100 mg/mL was 100% after 60, 40 and 30 min of exposure, respectively. In addition, Baqer *et al*. reported high scolicidal activity of *Z. officinale* against protoscolices *in vitro* and *in vivo* (54, 55). The methanol extract of *Z. officinale* rhizomes was reported to possess significant antibacterial activities. Bioactive compounds such as gingerols are responsible for antibacterial activity and perhaps scolicidal activity of *Z. officinale* (53, 56). Other responsible agents funded in *Z. officinale* are shogaol, diarylheptanoids, phenylbutenoids, flavanoids, diterpenoids and sesquiterpenoids (53, 57-59).

Angozeh (*Ferula assafoetida*)

Ferula assafoetida is a herbaceous plant of the umbelliferae family with the Persian name Angozeh. The species grows wild in deserts of Iran, mountains of Afghanistan and India (56). Several medicinal properties of this plant have been reviewed by Mahindra and Bisht (56). Kavoosi *et al*. indicated that 60µg/mL of essential oil from *F. assafoetida* killed all protoscolices after 10 min of exposure (21). Their results showed that main components of *F. assafoetida* were E-1-propenyl-sec-butyl disulfide, β-ocimene and β-pinene (21). However, scolicidal and antibacterial mechanisms of *F. assafoetida* or essential oils bearing disulphide compounds did not currently known and need more investigation.

Moreover, several studies have reported scolicidal activity of some other plants such as methanolic fruit powder extract of, *Myrtus communis, Satureja Khuzestanica, Olea europaea, Nigella sativa* L., *Mallotus philippinensis, Satureja khuzistanica, Salvia officinalis* and *Thymus vulgaris*. The results of these studies showed that all investigated plants have dose- and time-dependent effects against protoscolices of *E. granulosus* (60-64). The all procedures to determine the primary and secondary viability of protoscoleces in the above studies were similar and in following manner; 1) evaluation of viability of protoscoleces by eosin 0.1% dye test (1g eosin powder in 1000ml distilled water), 2) The viability was confirmed prior and after the experiments by checking the movement and activity of the flame cells of protoscoleces and staining of the protoscoleces., 3) The dead protoscoleces stained with eosin (red) but a living protoscoleces remains unstained (Fig. 1) (65).

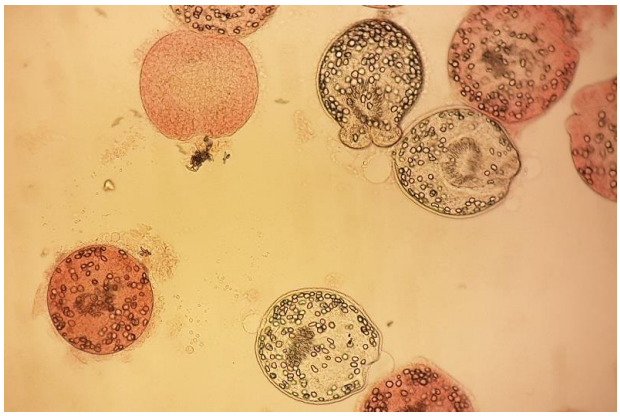

Fig. 1. Microscopic images of Eosin-stained (dead) and non-stained (live) protoscoleces after exposing with plants products.

According to the World Health Organization (WHO) Informal Working Group on Echinococcosis, a good and safe scolicidal agent is defined as acting in a short period of time (under 15 minutes), being effective in low concentrations, being stable in cyst fluid, not affected by dilution with the cyst fluid, being able to kill the scolex in the cyst, being nontoxic, having low viscosity, and being reading available and easily prepared as well as inexpensive (66-68). To date, many scolicidal agents were used for this purpose but no known any agent has all the above-mentioned properties (68).

Conclusion

In conclusion, our review demonstrated that traditional plants and their products might have high scolicidal activity that could be helpful in inactivation of the scolex in pre-, intra- and post-operative. However, the accurate mechanisms that plant extracts killed protoscolices are unclear and needed to more investigations. Another problem is safety of these extracts for human cells. Thus, many of these studies reported in literature are incomplete and more *in vivo* and cell culture investigation are needed to determine the safety of these plant extracts for human cells.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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