

Review Article

Efficacy of Thymol on the Scolices of Hydatid Cyst

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Abstract

As one of the major constituents of medicinal plant extracts, thymol has remarkable anti-worm properties. The contents of 5 English databases, including Scopus, PubMed, Web of Science, Embase and Google Scholar in the time span from 2008 to December 2019 were searched. All the relevant studies with English abstracts were searched regardless of the language of their discussions. Words and terms are used as syntax with specific tags from each database. Eleven out of 2146 studies were found eligible for evaluation. The findings indicated that 100% of the studies were about hydatid cysts and thymol. Moreover, 6 in vitro (55%) and 3 in vivo studies (27%), as well as 2 studies both in vitro and in vivo (18%), were carried out. According to these studies, thymol, as one of the major constituents of plant compounds, has a significant role in killing and reducing the parasitic protoscolex in vitro and in vitro. Likewise, thymol could have significant effects on restructuring protoscoleces and ultimately on their mortality. Thymol has an anti-hydatid cyst effect with the least side effects, and could be a good alternative to the treatment and prevention of anti-protoscoleces infections or in other studies against other helminth infections.

Keywords: *Echinococcus granulosus*, Thymol, In vivo, In vitro

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Introduction

Hydatidosis is one of the most important helminthic diseases caused by *Echinococcus granulosus* (*E. granulosus*). The intermediate hosts of *E. granulosus* are a wide range of herbivores, and humans are accidentally infected with hydatid cysts (1). The highest rates of human infections have been reported in the rural areas of eastern and southern Europe, the Mediterranean coasts, the Middle East, Latin America, and Africa. This disease is widespread in

almost all the tropical and subtropical regions of the world, particularly in areas where humans and dogs frequently come into contact (2). Surgery using the PAIR (Puncture, Aspiration, Injection, and Respiration) technique is one of the first and the best options in the treatment of this disease. Various chemical anti-protoscoleces drugs are used during the surgery to prevent the formation of secondary cysts which often have adverse effects on the tissue of the healthy organ in an infected person (3). The release of hydatid fluid containing protoscoleces during the surgery is the most

important cause of recurrence. To date, various anti-protoscoleces solutions have been used in the surgery and subcutaneous procedures (4). Hypertonic salt solution, silver nitrate, cetavlon, and formalin are the most common anti-protoscoleces agents every one of which might cause serious complications such as bile duct fibrosis and hepatic necrosis (4). Hence, World Health Organization has declared the urgent need to find a new anti-protoscoleces agent with more efficacy and less side effects (4).

Since they occur naturally and have homologous medicinal compounds, herbal medicines are more compatible with the body and lack unwanted side effects. Hence, their consumption could be a new approach (5). The medicinal properties of aromatic herbs are partly attributed to their essential oils. To date, the use of essential oils has been offered as a valuable treatment option against a number of diseases (6).

Pure oil-derived compounds such as carvacrol, eugenol, linalool and thymol, inhibit a variety of microorganisms such as bacteria and fungi (7). Moreover, several essential oils and their compounds have anti-parasitic activity. Thymol (2-isopropyl-5-methyl phenol) is one of the most important constituents of *Thymus vulgaris* (*T. vulgaris*) and *Origanum vulgare* essential oils and is a widely known antimicrobial substance (9). The in vitro and in vivo activities of thymol against *Leishmania panamensis* (10) and the larvae of *Anisakis simplex* have been demonstrated (11). Furthermore, new researches have been conducted on the treatment of the protoscoleces of hydatid cysts in vitro (12, 13). Thymol causes larval stage changes, critical changes, and the alteration of the morphological structures of cestodes. Hence, this review study aims to explain the research on new therapies and the treatment of hydatid cyst infections using herbal extracts one of the most important constituents of which is thymol. The anti-worm mechanism of these substances depends on the treatment with effective thymol compounds.

Materials and Methods

Search strategy

The present study was carried out according to PRISMA guideline (14) and was registered in the CAMARADES-NC3Rs Preclinical Systematic

Review and Meta-analysis Facility (SyRF) database. The search was performed in five English databases, including Scopus, PubMed, Web of Science, Embase, and Google Scholar up to December 2019. Studies in any language were entered in the search step if they had an English abstract. The words and terms were used as syntax with specific tags of each database. The searched words and terms were *E.granulosus*, Thymol, in vitro, in vivo and helminths

Selection of Studies

The studies in which the effect of thymol on cystic echinococcosis or protoscoleces echinococcosis was measured were examined. First, the studies were imported to EndNote X7 software (Thomson Reuters, New York, NY, USA), and duplicate studies were deleted. Afterwards, three independent authors examined the titles and abstracts of the studies and the relevant studies were included for further analysis. The same authors carefully read the studies, and the eligible studies with adequate inclusion criteria were selected (Fig- 1). The corresponding author resolved any disagreement between the authors. Moreover, the studies with inadequate information, those that were only abstracts, the ones that failed to match the methods with the results, and finally the studies with the incorrect interpretation of the results were excluded from the present research.

Data Extraction

Three independent authors extracted information from the selected articles and, if needed, the differences were resolved by the corresponding author. The extracted data include preparation, organism (strain), concentration, exposure time, the type of animals and significant results (Table 1 and 2).

Results

The procedure for selecting the studies has been shown in Figure 2. Accordingly, 2146 articles were selected in the search step, of which 11 eligible articles were included for examination. The findings indicated that most of the studies (100%: n=11) had been conducted on echinococcosis. Furthermore, 11 studies (100%) had been carried out on Thymol Preparation. Moreover, 6 studies (55%) had been performed in vitro, 3 studies (27%) in vivo and 2 studies (18%) both in vivo and in vitro. Further details have been presented in Table 1.

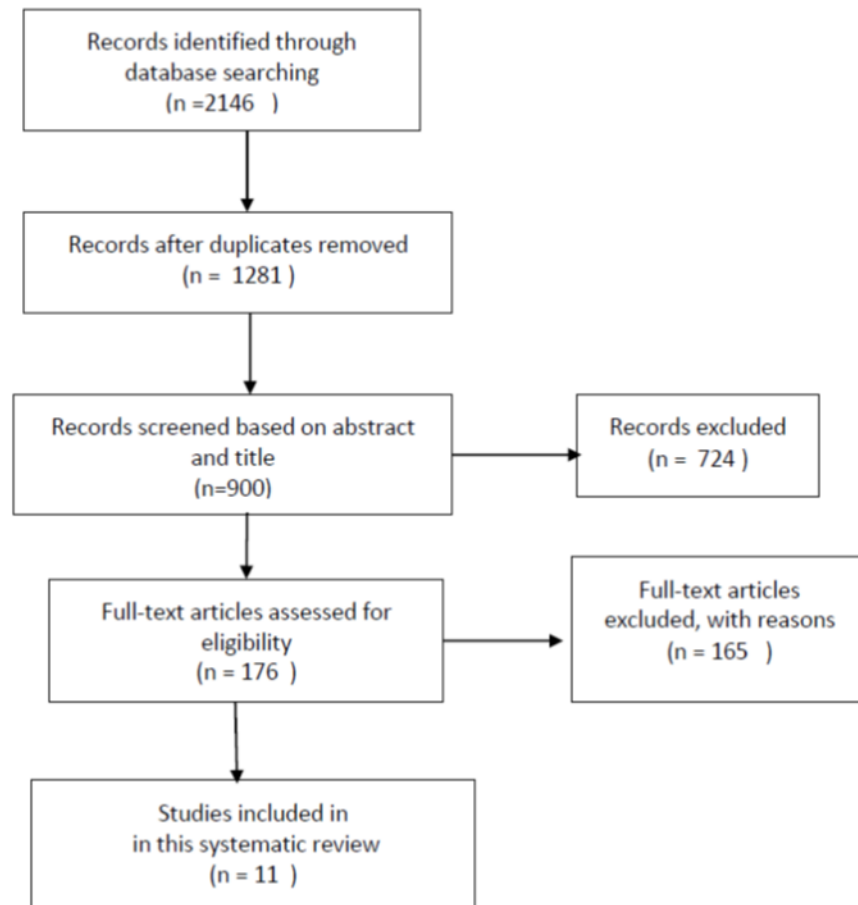


Figure 1. The in vitro Efficacy of Thymol on Scolices of Hydatid Cyst.

Discussion

Different anti-protoscoleces solutions have been used in the surgery and subcutaneous method (24). However, no ideal substance that might be completely effective and also without side effects has been identified so far (24). Formalin is one of the oldest substances frequently used in the past. Despite the efficacy of this substance on the protoscoleces, its use has long been discontinued due to its toxic effects and severe adverse effects on the bile ducts (4). Liver complications of 95% ethyl alcohol appear after 15 minutes. The salt solution at 10% has no anti-protoscoleces effect for the first 5 minutes, but it has

anti-protoscoleces effect at 20% concentration. Hepatic complications have also been reported at its 20% concentration. Hydrogen peroxide has a 100% anti-protoscoleces effect after 15 minutes of exposure but is not used today due to its side effects (25). Cetavlon has a low anti-protoscoleces effect of up to 0.1% at low concentrations, but due to numerous complications, including metabolic acidosis and globinemia, it is not used today (26). Therefore, the need to find a new and suitable anti-protoscoleces agent with the following properties seems necessary: being non toxic, having minimal side effects, causing the disappearance of protoscoleces at low doses and in the short term, being stable in the hydatid liquid, and finally being easy to prepare, available and inexpensive (27). The

antimicrobial compounds of medicinal plants are killing microorganisms (28). nowadays evaluated as alternatives to chemicals in

Table 1: The In vitro Efficacy of Thymol on Scolices of Hydatid Cyst.

Family and botanical name	Preparation	Organism (strain)	Concentration	Exposure time	Result	
-	Thymol	<i>E. granulosus</i>	100-250µg/ml	2,5,10 and 20 min	After 2 min of exposure to thymol, the viability of protoscoleces was approximately 1.3% at the concentration of 250 g/m	(12)
-	Thymol	<i>E. granulosus</i>	1,5 and 10 µg/ml	1-86 days	At the 18 day, the p.i., loss of morphology was markedly observed; some protoscoleces had lost their hooks, and the tegumental sucker region appeared to be altered, with several blebs and microtriches not being detectable in the surface	(13)
<i>Thymus vulgaris</i>	Thymol	<i>E. granulosus</i>	10 µg/mL	0-60 days	The viability of protoscoleces to 35.3 ± 2.8% after 60 days	(15)
<i>Origanum vulgare</i>	Thymol	<i>E. granulosus</i>	10 µg/mL	0-60 days	the viability of protoscoleces to 22.3 ± 1.2% after 60 days	
<i>Zataria multiflora</i> Boiss (Lamiaceae)	Thymol	<i>E. granulosus</i>	12.5- 100 µg/mL	5,10,20 and 30 min	thymol and as the main component of <i>Z. multiflora</i> essential oil at the concentration 100 µg/mL killed 100% protoscoleces after 5 minutes incubation	(16)
<i>Zataria Multiflora</i>	Thymol	<i>E. granulosus</i>	Unknown	1, 2, 3, 4, and 5 min	The scolicial power of <i>Z. multiflora</i> AW was 100% after 5 min	(17)
-	thymol	<i>E. granulosus</i>	1, 5, and 10 µg/ml	7 days	At the 7 th day , thymol 5 µg/ml caused a reduction in cell viability of 63%	(18)
<i>Trachyspermum ammi</i> L(Ajowan EO)	thymol	<i>E. granulosus</i>	3,5 and 10mg/ml	10,20,30 and 60 min	Ajowan EO at the concentration of 5 mg/mL killed 51.89, 72.20, 88.64 and 100% of protoscoleces after 10, 20, 30 and 60 min, respectively	(19)
-	thymol	<i>E. granulosus</i>	1,10 and 50 µg/ml	0-15 days	protoscoleces treated with thymol at the concentration of 50 µg/ml died at day 5 PT	(20)

					($P < 0.05$)	
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Table 2: The in vivo Efficacy of Thymol on Scolices of Hydatid Cyst.

Family and botanical name	Preparation	Organism (strain)	Animals kind	Concentration	Exposure time	Result	ref
Thymol	thymol	<i>E. multilocularis</i>	Mice (CF1)	40 mg/kg	20 days	The treatment with thymol or the combination of ABZ + thymol led to a significantly reduction in cyst weights	(21)
Thymol	Thymol	<i>E. granulosus</i>	Mice (CF1)	250, 200, 150 and 100 g/ml.	5 and 30 min	Loss of cyst turgidity and appearance of collapsed cysts	(12)
<i>Thymus vulgaris</i>	Thymol	<i>E. granulosus</i>	Mice (CF1)	10 μ g/mL	60 days	Protoscoleces incubated with <i>T. vulgaris</i> developed an average of 0.29 ± 0.4 g of cysts. However, the weight of cysts recorded in mice inoculated with <i>T. vulgaris</i> treated protoscoleces was significantly lower ($P < 0.05$) than that obtained in the control group	(15)
<i>Origanum vulgare</i>	Thymol	<i>E. granulosus</i>	Mice (CF1)	10 μ g/mL	60 days		
Thymol	Thymol	<i>E. granulosus</i>	Mice (CF1)	40mg/kg	24 h over 20days 12 h over 10 days.	Wet weight (g) of cysts Chemoprophylactic efficacy Thymol group I= 2.9 ± 2.3 Thymol group II= 3.7 ± 2	(22)
Thymol	Thymol	<i>E. granulosus</i>	Mice (CF1)	40mg/kg	24 h over 20days 12 h over 10 days.	Clinical efficacy Thymol group I= 4.5 ± 3.7 Thymol group I= 5.9 ± 2.4	

<i>Zataria multiflora</i>	Thymol	<i>E. granulosus</i>	Mice (BALB/c)	20 ml/liter	8 months	Wet weight (g) of cysts Chemoprophylactic efficacy Z. multiflora AW group=0 Therapeutic trials	(23)
<i>Zataria multiflora</i>	Thymol	<i>E. granulosus</i>	Mice (BALB/c)	40 ml/liter	30 days	Z. multiflora AW group=0.036	

Thymol is one of the main constituents of thyme essential oil with a wide range of antimicrobial properties. Elissondo *et al.* (2013) indicated that the viabilities of protoscoleces treated with thymol at 200 and 250 µg / ml for 2 minutes were 1.3% and 14.6%, respectively. On the other hand, the lesions with the changes of the body's tegument and scolex area of the thymol-treated protoscoleces between 2 and 10 minutes were clearly evident, while cyst treatment of mice treated with thymol showed changes including cyst incompatibility and cyst degradation and destruction in different minutes (12). Thymol causes damage to the tegument, the disruption of the rostellum, loss of the hook, and mitochondrial degradation *in vitro*. Furthermore, bleb formation and extensive wrinkling were observed in protoscolex structure at different concentrations in cysts treated with thymol (13). Investigations on the essential oil of *T. vulgaris* and *Origanum vulgare*, which is mainly composed of thymol, showed the effect of the essential oil on the protoscoleces and the germinal layer of the hydatid cyst as if the studies performed by electron microscopy or SEM indicated the destruction of the germinal cells treated with essential oil and also the degradation of the protoscoleces tegument as well as the leakage of the mitochondria of the rostellum region (15). The study conducted by Mahmoudvand *et al.* (2017) showed that the thymol found in *Zataria*

multiflora Boiss oil extract at 100µg/ mL caused 100% death of protoscoleces within 5 minutes (16). The aromatic extract of *Zataria multiflora Boiss* with 66.9% thymol was capable of inducing the 100% mortality of hydatid protoscoleces within 5 minutes *in vitro* (17). Certain studies have indicated that thymol at the concentration of 5µg/ mL for 7 days could reduce 63% of hydatid cell viability, and on the other hand the cells treated with thymol at 10µg/ mL for 7 days caused morphological changes such as wrinkle, cellular shrinkage and the decrease in the number of hydatid cells (18). Research conducted on AJOWAN oil, one of whose major constituents is thymol, suggests that 5mg/ml of essential oil causes 100% mortality of protoscoleces hydatid cyst after 60 minutes, which is associated with the highly potent anti- protoscoleces activity of thymol of the essential oil (19). The research carried out by Younes *et al.* (2012) showed that the treatment of protoscoleces by thymol at the concentrations of 1 to 10µg/mL resulted in the 100% mortality of all protoscoleces after 6 or 7 days, while the treatment of protoscoleces with Albendazole led to 100% mortality after 10 days (20). The research conducted by Albania *et al.* (2015) showed that the concurrent use of Albendazole and thymol for the treatment of mice infected with *E. multilocularis* strain for 20 days at 0.2 ml concentration reduced the weight of hydatid cyst by 1.5 ± 1.4 g.

(83.46%) in these groups, whereas in the group of mice treated with Albendazole suspension for 20 days, the mean cyst weight was 4.69 ± 1.48 (48.9%). On the other hand, the examination of the protoscoleces of the mice treated with thymol and Albendazole by the SEM procedure indicated the wrinkling and destruction of the protoscoleces structure (21). The chemoprophylactic effects of thymol on the weight of cyst of a group of mice treated for 20 days with a dose of 40mg/mL as a single dose every 24 hours with thymol compared to a group of mice that were treated with thymol for 40 days with a dose of 40 mg/mL every 12 hours indicated the reduction in cyst weight in the group treated for 20 days in comparison with the other groups. On the other hand, the therapeutic effects of thymol in mice 6 months after infection with protoscoleces with thymol for 20 days at a single dose of 40 mg/mL every 24 hours resulted in the mean cyst weight of 4.5 ± 3.7 , whereas in mice treated with Albendazole the cyst weight was 2.8 ± 2.9 g (22). The research on the impacts of the aromatic extract of *Zataria multiflora* (*Z. multiflora*), which is one of the major constituents of this plant, on the groups of mice infected with protoscolex have been preventive trials and therapeutic trials. In the present study, the mice preventively treated with the aromatic extract for 8 months daily did not develop hydatid cyst. On the other hand, the therapeutic efficacy of the aromatic extract of *Z. multiflora* in a group of mice treated with 40 mL/liter of the extract after 8 months of infection induced by protoscolex for 30 days was investigated. The mean cyst weight in this group was 0/036 g, and the size of the hydatid cyst was 3.10 mm, whereas it was 6.72 mm in the control group that had not been treated with the aromatic extract (23).

Limitations

1. Broader and more comprehensive in vivo studies on the use of medicinal plants for the treatment of human infections caused by hydatid cysts are required.
2. The use of nanoparticles due to properties such as the controlled delivery of drug to the target organ, low toxicity, increased drug uptake, and increased efficacy in the treatment of hydatid cysts should be considered as therapeutic objectives in the management of hydatid cysts.
3. In vitro and in vivo studies are required to fully evaluate the potential of herbal extracts or some of

their pure components as suitable options for the treatment of hydatidosis.

Conclusion

Today, parasitic diseases, including helminth diseases, are controlled by synthetic drugs, which have significant disadvantages such as high cost, drug resistance, environmental pollution, etc. Hence, the replacement of new therapies such as the use of traditional medicinal plants is on the rise. Accordingly, based on the results of the studies mentioned above, the high efficacy of the herbal medicines containing thymol as one of their main constituents indicates that short treatment periods at different doses in in vivo studies for the treatment of hydatid cysts is sufficient to achieve a therapeutic effect due to the lack of thymol toxicity. Moreover, thymol could be used as an efficacious alternative for the treatment of human hydatidosis. Therefore, further studies are required with regard to dose adjustment and duration of treatment in order to investigate the efficacy of the drug in the treatment of hydatid cysts.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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