A review of the effect of medicinal plant on helminthic infections

Faham Khamesipour,[1] Parya Kheyri,[1,2] Shadan Shojaat,[1] Bahareh Chelgerdi Dehkordi,[1] Bahareh Basirpour,[3] Sana Sadat Afzal,[1] Sakineh Akbari,[3] Seyed Hossein Hejazi[3,4]

[1]Shahrekord Branch, Islamic Azad University, Shahrekord; [2]Young Researchers and Elite Club; [3]Department of Parasitology and Mycology; [4]Skin Diseases and Leishmaniasis Research Center, Department of Parasitology and Mycology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Nowadays, parasitic worm infection is one of the most critical global health problems. Worm infections cause severe detriments to the livestock industry and also it can cause irreparable damages to immunocompromised persons. Therefore, the present study aimed to review conducted research on the treatment of worm diseases using medicinal plants' extract. In this systematic review, seven databases including 4 English (Scopus, PubMed, ScienceDirect, Google Scholar) and 3 Persian databases (Magiran, ISC, SID) were obtained between 2008 and 2020 to evaluate conducted studies related to the aim of the current review. Most of the studies focused on the *Balanites aegyptiaca* and *Carica papaya* plant. Water was the most common solvent (38.1%) and then it was methanol. The most studied parasite was *Haemonchus contortus* (35.5%), followed by *Aacharidia galli* (10.5%). Studies showed that plant extracts could reduce effect of worm infections in the host compared to synthetic drugs. Plant extracts can produce a medicine based on natural compounds and effective on worms with fewer side effects than synthetic drugs.

Correspondence: Parya Kheyri, Faculty of Veterinary Medicine, Shahrekord Branch, Islamic Azad University, Shahrekord, Iran, P.O. Box 166.
E-mail: kheyriiparya@gmail.com

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Introduction

One of the most critical health problems is parasitic worm infection that negatively affects third-world countries' social, health, and economic conditions.[1] Serious detriments have caused worm infections to the livestock industry with symptoms such as weight loss, decreased milk, meat, and wool production. Most importantly, these infections can also cause irreparable damages to immunocompromised individuals.[2-4] Today, various anthelmintics used to control worm infections have significant benefits in reducing worm load. However, these medicines' efficiency has been decreased due to medicinal resistance.[3-4] Because of the continuous use of anthelmintic. Interest in medicinal plants or their compounds in modern research against worm infection is increasing due to inaccessible and expensive synthetic drugs. Traditional medicines can be used as effective anti-worm treatment in many human and livestock populations because of easy access and appropriate effect. Within this framework, medicinal plants and herbal derivatives have been used as anti-worm treatments over the years by people.[4,5] The appropriate anthelmintic should have an available range and clinical therapeutic ability, including being taken as a single dose, no toxicity in the host, and low cost. Currently, none of the synthetic drugs have such properties. Side effects of synthetic drugs include nausea, digestive disorders, and dizziness.[6] According to the World Health Organization, 60% of developing countries still do not have anthelmintic medicines.[7] In developing countries, people still depend on different herbal remedies to treat worm infections, and herbal medicines and traditional treatments are the sources of health care to treat various diseases such as intestinal worm infection in these areas.[7] Thus, herbal remedies can provide an alternative to synthetic anthelmintic drugs and have fewer side effects and more efficacy than synthetic drugs; this indicates medicinal plant-based products to treat patients infected with worm infections.[8] Due to the increasing trend of patients with immunodeficiency worldwide, it seems necessary to screen them for infection with *Strongyloides stercoralis* and produce new medicines to treat such patients.[9] Several studies on worm models such as *Phertima posthuma*,[10] *Ascaridia galli*[11] due to physiological and anatomical resemblance with human intestin-

al nematodes and treatment with medicinal plants have been done. Therefore, it seems necessary to use medicinal plants in the prevention and emergence of new therapeutic approaches due to worm infection treatment. The present study aimed to investigate the research conducted to treat worm disease using medicinal plant extracts.

Material and Methods

Searching databases

In this study, search for resources in 7 databases including 4 English databases (Scopus, PubMed, Science Direct, Google scholar) And 3 Persian databases (scientific information database or SID, Magiran, and ISC) through the years of 2018 - 2020 and in Persian and English, to review the studies about the purpose of the present study. The combination of the words "Herbal medicine," "Extract," "*In vitro*," "*In vivo*," and "Parasitic helminths" were used to search.

Review and entry of studies

Studies in which the effect of a plant extract or its derivatives on one or more parasitic worms was measured were selected. First, analyses were recorded in Mendeley software version 7, and duplicate tasks were eliminated. Two independent authors then reviewed abstracts, and related articles were selected. The same two authors carefully read the selected studies, and the cases that met the inclusion criteria were added to the survey. Other studies were excluded from the study due to deficiencies in the required information, lack of access to the full text, non-compliance of methods with the results, and misinterpretation of the products. How studies were selected is shown in Figure 1.

Data extraction and analysis

Two independent authors extracted the required information from the selected articles and, if necessary, the difference between the two was resolved by the other author.

Results

Out of 3431articles selected in the searching phase, 76 of them were eligible for inclusion in the study. The results of this review study showed that most studies were focused on *Balanites aegyptiaca* and *Carica papaya*. Water (38.1%) and then Methanol (36.8%) were the most used solvents in extraction. *Heamonchus contortus* (35.5%) and then *Aacharidia galli* (10.5%) were the most studied parasites. The extracted information is given in Table 1.

Discussion

Recently, special attention has been paid to modern therapies using herbs to treat various diseases like parasitic infections. Numerous studies have been performed on anthelmintic and antiprotozoal effects of different plant extracts *in vitro* and *in vivo* conditions.[12-15] The present study examines the constant use of herbs, searching for new herbs, and their further production and effects and mechanisms of various extracts of herbs to replace with standard synthetic drugs.

Using herbs is a treatment for *Haemonchus contortus*

A gastrointestinal parasite that causes Haemonchosis disease. This parasite is found in the abomasum of goats and sheep. Economic losses resulting from Haemonchosis in tropical and subtropical areas often cause mortality and a reduction in livestock production and growth.[16] A study by Sambodo *et al.* showed that the crude aqueous extract of *Biophytum petersianum* has proper anathematic properties against *Haemonchus contortus*. In this study, a 10% concentration of this plant's aqueous extract in the 2-4 hours caused 100% death of worms. Also, in reviews using a scanning electron microscope (SEM), changes in the structure of worms like cuticle destruction, cervical protrusions loss, anterior part destruction, and posterior part shrinkage of the parasite in the 10% concentration of the aqueous extract of this plant were observed.[17] Von Son - de Fernex *et al.* showed antiparasitic properties of the tropical plants *Cratylia argentea, C. argentea veranda, Arachis pintoi, Gliricidia sepium*, and *Yacapani* against *Haemonchus contortus*. In this study, a concentration of 1,200 µg/mL of these plants' extract inhibited the molting and migration process of *Haemonchus contortus* larvae.[18] Also, effects of the aqueous extract of Annona leaf was studied against *Haemonchus contortus* in eggs, larvae, and adult stages in vitro environment that showed a high concentration of *A. muricata* extract affected Egg Hatching Test (EHT) and larval motility assay test (LMT) by 84.91% and 89.08%, respectively, which was related to Phenolic compounds in the plant.[19] A study of Castaneda Ramirez et al. examined *Acacia pennatula* vessels' role in Larval Escheatment Inhibition Assay test (LEILA). In this study, it was found that the less the age of the larval stage of *Haemonchus contortus* (L3) is, the less concentration of *Acacia pennatula* extract is required to inhibit escheatment; so 100 µg/mL in the first week and 200 µg/mL in the fifth week were efficient.[20] Using *Piper tuberculatum* and *Hura crepitans* extracts at EHT=9 affected Larval Development test (LD). *Lippia sidoides* had the best effect on EHT and LDT stage in inhibiting *Haemonchus contortus* larva growth.[21]

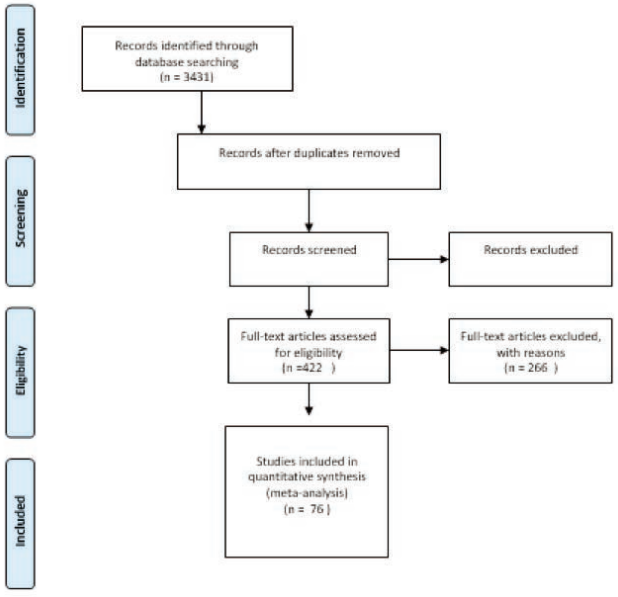

Figure 1. Flow chart of selection of relevant publications

Table 1. Extracted data from studies.

Plant name	Solvent	Parasite name	*In vivo /in vitro*	Results	Reference
Azadirachta indica (A. Juss.) *Annona squamosal(neem)* *Tobacco (Nicotiana tabacum)*	water	Nematodes in goats	*In vivo*	Revealed no reductions on day 10 post-infection in animals treated with herbal extracts.	[60]
Myrsine Africana (kechemo)	Hydroalcoholic	*Hookworm*	*In vitro* *In vivo*	80% of Hydroalcoholic extracts of M. Africans exhibited larvicidal activity. The LC50 was 217.77 microgram per milliliter The lethal dose (LD50) of the plant extract was beyond 2000mg/kg of body weight.	[61]
Mitragyna inermis (willd.) Kuntze	Powder of leaves	*Haemonchus contortus*	*In vivo*	The powder of *M. Inermis* leaves (> 60%) significantly reduced ($p < 0.01$) fecal egg counts in the three breeds of lambs.	[62]
Maytenus emarginata(willd.)Ding Hou	methanol water hydroalcohol	*Pheretima posthuma* *Ascaridia galli.*	*In vitro*	Peak activity Was exhibited by the methanolic extract at a concentration of 50mg/mL.	[63]
Ferula asafoetida (H.Karst.) *Allium sativum L.*	hydroalcoholic	*Strongylus spp.*	*In vitro*	Hydroalcoholic extract of F.asafoetida at a concentration of 10, 50, and 100 mg/mL killed over 90% of the larvae, and A. Sativum extract at the concentration of 50 and 100 mg/mL killed over 95% of larvae($p<0.05$).	[64]
Carica papaya L.	water ethyl acetate	*Pheritima posthuma* *Petroleum ether*	*In vitro*	Aqueous extract gave the highest extractive yield of 19.8%, followed by the ethyl acetate extract at 17.2%.	[65]
Saba Senegalensis (A.DC.) pichon	aqueous decoction (AD) hydroethanolic macerate(HEM)	*Heligmosomoides bakeri*	*In vitro*	HEM's ovicidal and larvicidal activity is more interesting than that of AD with an Emax = 95.60% and an IC_{50} = 390 µg/ML.	[66]
Gigantochloa apus (Schult.) Kurz	water	*Haemonchus contortus*	*In vitro*	The crude aqueous extract, looks more pointed. Morphometry study of *h. Contortus* indicates that it has a significant difference for body length, body width, cervical papillae, and spicule length in the male.	[67]
Cymbopogon citratus (DC.) Stapf	water methanol	*Haemonchus spp.* *Trichostrongylus spp.*	*In vitro*	Both extracts were active against Haemonchus spp. And *Trichostrongylus* spp. Larvae.	[68]
Saponins from *Medicago spp.*	Methanol	*Strongilus*	*In vitro*	With 1.72 mg/mL EC50 and 3.84 mg/mL EC90, a saponin from M. Polymorpha cultivars Anglona was the most active.	[69]
ginger *(Z. officinale)*	ethanol	*Protoscolices of hydatid cyst*	*In vitro*	There was no significant difference between the three concentrations of 200, 150, and 100 mg/mL ($P>0.05$).	[70]
schleichera oleosa (Lour.)	ether water ethanol chloroform acetone	*Eisenia fetida* *Excavates* *Perionyx* *Pheretima* *Posthuma* *Ascaridia galli*	*In vitro*	Significant anthelmintic activity was established by the ethanolic and aqueous extracts. Inhibition of alpha-amylase by ethanolic and aqueous extracts was significant with the IC_{50} value of 36.63 and 73.94 µg/mL, respectively, compared to standard acarbose.	[71]
Areca catechu L.	water	*Ascaridia galli*	Both	The extract damaged the morphology of *A. Galli in vitro*. The average eggs per gram decreased from 1485±386.62 to 0±0.00 during 14 days of treatment of 79 mg/mL of extract *in vivo.*	[72]
Balanites aegyptiaca (L.) Delile	methanol	*Toxocara canis*	*In vitro*	The main changes induced by treatment with the tested extract were wrinkled cuticular surface and deformed sensory papillae.	73]
Albizia gummifera (J.F.Gmel.) C.A.Sm. *Phytolacca dodecandra L'Hér.* *Vernonia amygdalina Del.*	hydroalcoholic	Ovine GIT nematodes	*In vitro*	All three plant crude extracts were inhibited egg hatchability significantly ($p< 0.05$) as compared with the negative control but the inhibition among them was not significantly different in the effect.	[74]
Cassia spp.	n-hexane ethanol	*Haemonchus contortus*	*In vitro*	The movement of *H. Contortus* larvae was significantly inhibited after exposure to Among the species of Cassia, the C. Surattensis (at 200 mg/mL) showed the highest ($p < 0.05$) inhibition level on the larvae.	[75]
Camellia sinensis (L.) Kuntze	Ethanol	*Haemonchus contortus*	*In vitro*	Both *A. Lebbeck* and *C. Sinensis* exhibited 88% and 95% mortality at 6 & 8 mg/mL after 8 hours of treatment.	[76]
Albizia lebbeck (L.) Benth *Bridelia ferruginea Benth* *Combretum glutinosum Perr. ex DC.* *Mitragyna inermis (Willd.) Kuntze*	Methanol acetone	*Haemonchus contortus*	*In vitro*	At the highest concentration (2400 µg/mL), all adult worms were motionless after 24 h of exposure, while at the lowest concentration (< 150 µg/mL), this occurred after 48 h of exposure. M. Inermis and C. Glutinosum extracts were more effective than B. Ferruginea extracts ($p < 0.05$).	[77]
Syzygiumaromaticum (clove)	water	*Hymenolepisnanain*	*In vivo*	The extracted oil's lethal and therapeutic doses were also calculated as 225 and 2.25mg/kg.	[78]

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Table 1. Continue from previous page.

Plant name	Solvent	Parasite name	*In vivo /in vitro*	Results	Reference
Syzygiumaromaticum (clove)	water	*Hymenolepisnanain*	*In vivo*	The extracted oil's lethal and therapeutic doses were also calculated as 225 and 2.25mg/kg.	[78]
Carica papaya	methanol	Indian earthworms Cattle worms	*In vitro*	The result indicated that the Papaya seeds lead to paralysis of earthworm and death.	[79]
Jasminum sessiliflorum (Vahl)	ether chloroform ethyl acetate ethanol	*Earthworm* *Pheretima posthuma*	*In vitro*	The ethanolic extract was found to produce the highest degree of positive response.	[80]
Ocimum sanctum L.	ethanol	*Ascaridia galli*	*In vitro*	The results were LC50 of Ocimum sanctum Linn. Leaves ethanol extract was 7.9% at 4 hours, 3.7% at 6 hours, 1.8% at 8 hours, and 0.8% at 10 hours, and the LC90 was 8.4% at 10 hours.	[81]
tobacco (Nicotiana tabacum)	waret	*Ascaridia galli*	*In vitro*	Scanning electron microscopy of tobacco infusion-treated nematodes showed extensive structural damage.	[82]
Cymbopogon citratus (DC.) Stapf	essential oils (CcEO) nanoemulsion (CcEOn)	Haemonchus contortus	*In vivo* *In vitro*	In the egg hatching test, cceo and cceon (1.25 mg/mL) inhibited larval hatching by 98.4 and 97.1%, respectively. Three animals treated with cceo died whereas in the group treated with cceon one animal died.	[83]
Hypoestes forskaolii (Vahl)	n-hexane methanol chloroform	*Trichostrongylus spp* *Chabertia ovina* *Cooperia spp* *Haemonchus contortus* *Teladorsagia spp*	*In vitro*	The n-hexane extract has a percentage of inhibition of egg hatching greater ($p < 0.05$) than other extracts inhibiting the 30.8% at the concentration of 1 mg/mL.	[84]
Carica papaya L.	hexane	*Strongyloides venezuelensis*	*In vitro*	The extract inhibited egg hatching with high efficiency at concentrations of 56.6 mg/mL (95.74%) and 5.66 mg/mL (92.16%).	[85]
Artemisia herba-alba Asso *Punica granatum L.*	methanol	*Haemonchus contortus*	*In vitro*	The highest concentration (10 mg/mL) of all the extracts caused a significantly ($p<0.05$) nematocidal activity. Maximal (98.67%) egg hatching inhibition effect was exhibited by the flower extract of *A. Herba-alba* at 1mg/mL.	[86]
Lantana camara (L.) *Tamarindus indica L.*	methylene chloride methanol hexane	*Onchocerciasis*	*In vitro*	The highest activity against was observed with the hexane extract of *L. Camara l*eaves (lclhex), with IC_{50} of 35.1 µg/mL for adult females and 3.8 µg/mL for the mf. This extract was more active than L. Loa mf.	[87]
Terminalia Catappa (Linn)	ether ethyl acetate methanol Water Dichloromethane hydroalcoholic	*Haemonchus concortus*	*In vitro*	The dichloromethane extract displayed the highest egg hatch inhibition percentage of 98.94% at 6.25mg/mL and also showed 100% larval reduction at a concentration of 12.5mg/mL after 3 days and 98.9% at the least concentration of 6.25 mg/mL. While the methanol extract showed the lowest inhibition of 95.77% at the same concentration	[88]
Curcuma longa L	Water methanol	Gastrointestinal nematodes	*In vivo*	Revealed ED50 for egg hatch was 0.594 indicates a high degree of resistance towards benzimidazole in goats prevailed in the farm.	[89]
Azadirachta indica(A.Juss.)	chloroform hexane ethyl acetate n-butanol	*Haemonchus contortus*	*In vivo*	There was no significant difference statistically ($P>0.05$) in FECR% (45.62 vs 85.14) in sheep at low and high doses of the plant.	[90]
Ocimum gratissimum L.	acetone	*Haemonchus placei*	*In vivo*	The best-fit LC50 values, found to be significantly different (alpha < 0.0001), were 17.70 mg/mL and 56.04 mg/mL for C. Citratus and O. Gratissimum, respectively.	[91]
Cymbopogon citratus (DC.) Stapf	essential oil (CLEO)	*Protoscoleces of hydatid cysts*	*In vitro* *ex vivo*	Although CLEO at the doses of 50, and 100 µL/mL exhibited no similar effect in the ex vivo analysis; but, at the dose of 200 µL/mL and an exposure time of 5 min, approximately 100% of cysts	[92]
Terminalia bellerica *Terminalia chebula* *Terminalia catappa*	Hexane Chloroform Methanol Acetone	*Setaria cervi*	*In vitro*	T. Bellerica, t. Chebula and t. Catappa showed a decline in the motility of the worms at higher doses of 5 and 10 mg/mL after 4 h of incubation, whereas dec (diethylcarbamazine) worms were active at all the doses upto 4 h and further after 24 h followed by mtt reduction assay.	[93]
Murraya koenigii (L.) Spreng.	Methanol n-hexane chloroform n-butanol water	*Haemonchus contortus*	*In vitro*	Subfractions (SF), SF 3, and 11 of the chloroform fraction showed better ovicidal activity whereas SF 2,6,7,32 and 37 showed the best larvicidal activity. The larvae that were used for testing the larvicidal activity, were found to be sluggishly motile after half an hour of incubation with the extract and were progressively dead in a dose-dependent manner.	[94]
Maytenus senegalensis (Lam.) Exell	water	*Haemonchus contortus*	*In vitro*	For the LMI assays, the aqueous extract of M. Senegalensis showed a significant ($p <0.05$) inhibition of larval migration in a concentration-dependent manner. The highest concentration used (2400 µg.mL– 1) showed a 37.77% inhibition.	[95]

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Table 1. Continue from previous page.

Plant name	Solvent	Parasite name	*In vivo /in vitro*	Results	Reference
Origanum aciculare (Waldst. & Kit.) Kuntze. *Cinnamomum verum J.Presl* *Rosmarinus officinalis L.* *Capsicum annuum L.*	water	*Haemonchus contortus*	*In vitro*	In EHT, LC50 values of HC and oxfendazole were 498 and 1.6 ppm, respectively. In AMA, 100% mortality of H. Contortus was observed after 6 hr of treatment with HC (100 mg mL-1) whereas two positive control groups could not kill all worms after this exposure time. These results indicated the anthelmintic potential of HC.	[96]
Dicerocaryum eriocarpum *Pappea capensis* *Aloe ferox* *Helichrysumsp* *Senecio congestus* *Senecio barbertonicus* *Gardenia sp.*	water	*Haemonchus* *Contortus*	*In vitro*	Larval mortality assays were carried out on the aqueous plant extracts at concentrations of 2.5 mg/mL, 5 mg/mL, and 7.5 mg/mL. Thiabendazole was used as a positive control. Extracts of all plant species demonstrated larval mortality abilities that were concentration and time-dependent.	[97]
ridax procumbens *linn belonging* *Asteraceae*	chloroform water	*Pheritima posthuma*	*In vitro*	The present study results indicated that the aqueous and chloroform extracts of leaves of Tridax procumbens linn show significant dose depending on the pharmacological activity on the Indian earthworms.	[98]
Embelia schimperi fruits	n-hexane Methanol	*Caenorhabditis elegans*	*In vitro*	The n-hexane extract exhibited significant anthelmintic activity against the model organism *C. Elegans.* The subsequent fractionation procedure resulted in two active fractions.	[99]
Dioscorea Mexicana Fruits	Ethanol	*Pherithima posthuma*	*In vivo*	The animal was given a dose of 0.04 mg/mL dose and it was found to be a low dose which has taken a long time for the paralysis conditions. 0.05 mg/mL as the lethal dose and has a perfect time for paralysis compared to low and high doses.	[100]
Zanthoxylum rhetsa	methanol	*Eisenia fetida (Annelida)* *Tubifex tubifex (Annelida)*	*In vitro*	The extracts exhibited significant anthelmintic activity as evidenced by a decrease in paralysis death time in the treatment groups when compared to standard.	[101]
Embelia ribes	Water	*Ascaridia galli*	*In vitro*	Methanolic extract of Embelia ribes showed a better inhibitory effect (61.23%) on the embryo nation of eggs of *Ascaridia galli* than its aqueous extract (58.20 %). Inhibitory effect of 77.66±1.85%.	[102]
Mangifera indica *Nauclea diderrichii (De Wild.) Merr.*	methanol Chloroform Acetone n-hexane	*Haemonchus placei*	*In virto*	The anthelmintic assay shows that acetone extract is worm-active with a best-fit LC50 of 16.24 mg/mL, while the chloroform extract was inactive. Fractionation of the acetone extract yielded three fractions (FA, FB, and FC), Only fraction B was active against *H. Placei* with LC50 of 12.24 mg/mL of the fractions.	[103]
Caesalpinia pulcherrima (Caesalpiniaceae)	Ether Dichloro methane ethyl acetate ethanol	Eisenia foetida	*In vitro*	All the extracts were found to be exhibited dose-dependent anthelmintic activity. The decreasing order of extracts activity was ethyl acetate, ethanol, dichloromethane, and petroleum ether extracts.	[104]
Citrus aurantiifolia (Christm.) Swingle	ethanol	*Pheritima posthuma* Asha	*In vitro*	Different concentrations (2.5, 5, 10, 20 mg/mL) of ethanolic extract of leaves of *Citrus aurantifolia swingle* were evaluated for *in vitro* anthelmintic activity. The percentage yield of ethanolic extract was obtained 10.5 & 7.3% w/w respectively.	[105]
Carica papaya L	ethanol	*Paramphistomum cervi* *Haemonchus contortus*	*In vitro*	Ethanolic extracts of the leaves of the *C. Papaya* responsible for the death of *P. Cervi* and *H. Contortus* especially at the higher concentration (100%) compared to the standard reference of Piperazine citrate.	[106]
cranberry vines(CV)	Water organic proanthocyanidin	*Haemonch* Us contortus	*In vitro* *In vivo*	CV treated worms were observed via scanning electron microscopy, and a preliminaryinvestigation of the efficacy of CV powder against experimental infection of *H. Contortus* was conducted. It was determined by administering 21.1 g CV powder to lambs for three consecutive days and collecting fecal egg count data for four weeks post-treatment. The effect of CV-PAC on egg hatching, L3 motility, and exsheathment was limited	[107]
Millettia pachycarpa Benth.	methanol	*Ascaridia galli*	*In vitro*	The roundworm showed extensive structural changes and damages.	[108]
Biophytum petersianum Klotzsch	water	Haemonchus contortus	*In vitro*	Crude aqueous extract of B. Petersianum caused changes in worm structure such as cuticle destruction, and loss of bumps of the neck.	[17]
Gliricidia *sepium (Jacq.)* *Cratyliaargentea Yacapan argentea Veranera*	water	*Haemonchus contortus*	*In vitro*	In this study, the 1211 µg/mL of plant extracts hindered the shelling and migration of Haemonchus Contortus.	[18]
Arachis pintoi C. *Annona muricata L.*	acetone water	*Haemonchus contortus*	*In vitro*	Annona muricata extract was 84.91%on EHT and 89.08% on LMT effective.	[19]

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Table 1. Continue from previous page.

Plant name	Solvent	Parasite name	*In vivo /in vitro*	Results	Reference
Annona muricata L.	water acetone	*Haemonchus contortus*	*In vitro*	200 and 100 µg/mL of Acacia oennatula Leave extract obstructed warm molting.	[20]
Piper tuberculatum	Ethyl acetate	*Haemonchus contortus*	Both	*Lippia sidoides* had the best effect on EHT and LDT stages on *Haemonchus contortuth* growth.	*[21]*
Hura crepitans *Lippia sidoides Carapa guianensis* *Menthe piperita* *Leonotis* *Occidentalis senna* *Leucas martinicensisocymifolia Albizia* *Rumex abyssinicus schimperiana*	ethanol Water Methanol	*Haemonchus contortus*	*In vitro*	Aqueous extract of *Leonotis ocymifolia* caused 100% growth inhibition in larvas.	[22]
Prunella vulgaris	methanol	*Haemonchus contortus*	*Both*	The most significant decrease in the number of eggs in the feces was in the group treated with the methanolic extract of *Prunella vulgaris.*	[24]
Onobrychis viciifolia	Acetone water	*Haemonchus contortus*	*In vitro*	Changes such as muscle cell breakdown, intestinal cell lysis, changes in Hypodermis, and abnormal chromatin density of epithelial cells were observed. Wounds and lesions also appeared on the surface of the worm.	[25]
Gliricidia sepium	acetone	*Cooperia punctate*	*In vitro*	After treatment with H-chrome-2-one-2 fractions, In TEM and SEM examination of eggs of the warm, Changes and fractures in the eggshell of *Cooperia punctate* was observed.	[27]
Leucaena leucocephala	Distilled water	*Cooperia punctate*	*In vitro*	In Treatment with TRIF3 fractions of *Leucaena leucocephala*, EHT was 90/49-+2/85.	[28]
Chenopodium ambrosioides	methanol Diethyl acetate	*Toxocara canis*	*Both*	Hexane extracts of *Chenopodium ambrosioides* reduce Inflammation in the lungs and liver of *Toxocara canis* infected mice in vivo and aqueous extract of *Nutridesintox* had the best effect *in vitro.*	[30]
Pycnanthus angolensis Nutridesintox	Dichloromethane	*Ancylostoma caninum* *hexane*	*Both*	150 µg/mL *Chenopodium ambrosioides* essential oil caused 100% . motionless in the larva	[32]
Chenopodium ambrosioides L *Vicia pannonica*	ethanol methanol	*Trichostrongylu*	*In vitro*	In this study, the Estonian extract caused severe damage to the larva.	[35]
Lysiloma *Pithecellobium Dulce (LAE) acapulcensi*	Distilled water	*Trichostrogylus* *Colbiformis*	*In vitro*	In this study, 250 µg/mL of LAE reduced warm growth by 32/6%. The larvicidal ability of *Pithecellobium* was less than *Lysiloma.*	[36]
Tanshinone II-A (TS II-A) *Cryptotanshinone(CPT)*	NR	*Angiostrongylus* *Cantonensis*	*In vivo*	Combination of Albendazole and Tanshinone II-A reduced neuritis in *Angiostrongylus cantonensis* infected mice.	[38]
Curcumin and ginger	methanol	*Ascaridia galli*	Both	Lethal dose 100mg/mL of both curcumin and ginger extract was up to 80% in48h for *Ascaridia galli.*	[11]
Balanites aegyptiaca	methanol	*Toxocara vitulorum*	*In vitro*	Treatment with 120 µg/mL methanolic extract of BAE made the cuticle surface wrinkled and the worm surface porous.	[43]
Balanites aegyptiaca	methanol	*Trichinella spiralis*	*In vivo*	1000 mg/mL/kg methanolic extract of *Balanites aegyptiaca* in 5 days caused a reduction in warm migration and Larval cysticide in rats.	[45]
Cynodon dactylon	methanol	*Hymenolepis diminuta*	Both	40 µg/mL of *Cynodon dactylon* in 4.12-+0.55 hours caused warm paralysis. Also in rat treatment with 800mg/mL/kg in 5 days caused a 77/64%decreas in the number of eggs in the feces.	[47]
Alpinia nigra	ethanol	*Fasciolopsis buski*	*In vitro*	20 µg/mL of ethanolic extract of *Alpinia nigra* in 2.14-+0.48 hour caused warm paralysis but in 3.94-+23 hour caused death in *Fasciola hepatica.*	[49]
Cajanus cajan *Lantana camara* *Bocconia* *Piper auritum* *Artemisia mexicana* *frutescens*	Methanol Ethyl acetate Hexane	*Fasciola hepatica*	*In vitro*	According to this study, the lethal dose of the 5 studied extracts Significantly had a lethal effect on the worm. P<0.05	[50]
Soybean	NR	*Fasciola gigantica*	*Both*	Soybean extract reduced liver damage due to *fasciola gigantica* and reduced caspase 3 in liver cells.	[52]
Allicin	NR	*Schistosoma mansoni*	*In vitro*	10 µg/mL of *Allicin* caused changes in surface tubercles and spins of the worm. Upper concentrations caused severe damages to the worm tegument.	[54]
Mentha x villosa Huds	Sodium sulfate	*Schistosoma mansoni*	*In vitro*	MVEO caused ultra-morphological changes on *Schistosoma mansony* and tegument distraction.	[55]
Clerodendrum umbellatum Poir	water	*Schistosoma mansoni*	*In vivo*	Treatment with 160 µg/mL of aqueous Leave extract caused 100% death in *Clerodendrum umbellatum poir.*	[56]
Dregea volubilis	methanol	*Paramphistomum microbothrium*	*In vitro*	100 µg/mL Methanolic extract of *Bombax malabaricum* in22.17_+.048 minutes caused death in *Paramphistomum explanatum.*	[58]
Balanites aegyptiaca	methanol	*Paramphistomum microbothrium*	*In vitro*	200 µg/mL Methanolic extract of the fruit of *Balanities aegyptiaca* Caused severe damages to the worm tegument.	[59]

A study of *Haemonchus contortus* larva EHT and LDT using a hydroalcoholic extract of *Senna Occidentalis* leaf, the aerial part of *Rumex abyssinicus*, *Leonotis ocymifolia, Albizia schimperiana*, and *Leucas martinicensis* stem bark showed that the aqueous extract of *Leonotis Ocymifolia* caused 100% growth of larvae. The best concentration of ED50 for EHT of aqueous and hydroalcoholic extract of *Leucas Martinicensis* was 0.09 mg/mL.[22] In a study, anthelmintic activities of an extract combination of *Indica azadirachta* leaf, *Nicotiana tabacum* (N.), *Calotropis procera* (C.) flower, and *Trachyspermum Ammi* seed were examined in EHT and Adult Motility Test (AMT) of *Haemonchus Contortus* worm. Accordingly, by increasing the compound concentration, the amount of EHT decreased. At a concentration of 50 mg/mL, only 1% of worms hatched; whereas, at a concentration of 0/02mg/mL, approximately 70% of the worms hatched. Within 6 hours, from 3.125 mg/mL to high, all worms died.[23] A study used the methanolic and aqueous extract of *Prunella vulgaris* to examine its anthelmintic properties against *Haemonchus contortus*. In this study, crude methanolic extract with LC50 (Lethal concentration of 50) equivalent to 2.48 mg/mL was used which showed more inhibitory effects on EHT than a crude aqueous extract with LC50 equal to 3.36 mg/mL. Also, the group treated with methanolic extract of *Prunella vulgaris* had the highest decrease in the number of eggs in the feces.[24] Brunet *et al.* studied the role of *Onobrychis viciifolia (Sainfoin)* extract in larva stage B L3 of *Haemonchus contortus* worm using morphological changes. Larval envelope structure at a concentration of 1200 mg/mL of *Sainfoin* extract using a Transmission Electron Microscope (TEM) shows changes such as muscle cell breakdown, intestinal cells breakdown, hypodermic changes, abnormal chromatin density of the nucleus of epithelial cells, and wounds and lesions created on the surface of the worm.[25]

The use of herbs for *Cooperia punctate*

This parasite is 5-9 mm long. In all species of this parasite, the head part is dilated and has transverse lines. Thick spicules, often with a wing-like dilation, are in the midline. The female parasite has a long tail, and its genital area is covered. The parasite lives in the small intestine of cows.[26] Von Son-de Fernex *et al.* Using the isolated component of *Gliricidia sepium* against *Cooperia punctata* worms showed that this extract inhibits the growth and egg hatching of *Cooperia punctata* worm (Half maximal effective concentration or EC50 equivalent to 0.024 0.082 mg/mL). Examining worm eggs with SEM and TEM revealed changes and fractures in parasite eggshell through treatment with H-chromene-2-one 2 component.[27] Also, the use of components derived from the aqueous extract of *Leucaena leucocephala* to conduct EHT and worm egg damages showed that the percentage of egg hatching inhibition in the LlC1F3 segment is equal to 90/49±2/85, which was higher than other components. Also, studying parasite eggs after treatment with LIC1F3 Fraction using SEM revealed the eggshell's disintegration and a formation of depressions and tears on the eggs' surface. Also, changes in electron density and thickening of the layer of worm eggs were observed by TEM.[28]

The use of herbs for *Toxocara canis*

Toxocara canis is a nematode that causes Toxocariasis disease in humans, which is caused by infection formed after consumption of *Toxocara canis* eggs in soils contaminated with dog feces. Children are more susceptible to this infection due to gluttony (Pica).[4,29] In a study, antiparasitic effects of *Pycnantha angolensis, Chenopodium ambrosioides,* and *Nutridesintox* extracts against *Toxocara canis* larva were evaluated. The results showed that the hexane extract of *Chenopodium ambrosioides* is more effective than other extracts in vivo environment and reduces inflammatory reactions caused by *Toxocara Canis* larva infection.[30]

The use of herbs for *Ancylostoma caninum*

Ancylostoma caninum is a hookworm that mainly causes diseases in dogs' small intestine. This worm infection shows a wide range of symptoms in dogs. Other hosts include carnivores such as wolves, foxes, and cats, and also a small number of diseases have been reported in humans.[31] In a study by Monteiro *et al*., the role of ethanolic extract and essential oil of *Chenopodium ambrosioides L* in controlling *Ancylostoma caninum* worms is discussed.[30] *Chenopodium ambrosioides* essential oil was effective in a concentration of 140 µL/mL against larva L3 and reduces the number of eggs per each gram of feces the aim of this study was quantitate the yield the chemical composition of the essential oil of *C. ambrosioides* and they found that as well as the in vitro effect of the ethanolic extract and the essential oil in L3 of *Ancylostoma spp* and the in vivo effect(s) of the essential oil in dogs. The effects of the ethanol extract and essential oil on *Ancylostoma spp* were observed in vitro by exposing larvae to the extract at concentrations ranging from 0.005 g mL-1 to 0.2 g mL-1 and to essential oil at concentrations of 50, 100, 150 µL mL-1.[32]

The use of herbs for *Trichostrongylus spp*

Trichostrongylus spp is a species of nematodes distributed among herbivorous animals worldwide. At least 10 species of *Trichostrongylus* are associated with human infections. The infection occurs through consuming infectious larvae in vegetables and contaminated water.[33] Today, anthelmintic resistance is expanding worldwide; therefore, manufacturing non-synthetic drugs seems necessary.[34] Kozan *et al.* investigated the anthelmintic role of *Vicia Pannonica* against *Trichostrongylus* parasites. In this study, aqueous, ethanoic, chloroformed, Estonian, and hexane extracts of *Vicia pannonica var. purpurascens* had a 100% effect on larval movements in 10th minute and all mentioned extracts damaged the larval sheath in this study they cover in vivo and in vitro tests that have been developed for the detection of nematode resistant to the main anthelmintic groups, but each suffer to some degree from reliability reproducibility, sensitivity and ease of interpretation.[35] Aqueous extracts of *Pithecellobium dulce* and *Lysiloma acapulcensis* had lethal effects on *Trichostrongylus clubriformis* eggs at concentrations of 250 and 500 µg/mL. Also, *Pithecellobium dulce* has lower larvacidal effects than aqueous extracts of *Lysiloma acapulcensis* and Levamisole.[36]

The use of herbs for *Angiostrongylus*

Angiostrongylus is a nematode parasite that can cause diseases in humans' gastrointestinal tract and central nervous system. *Angiostrongylus cantonensis*, called rat lungworm, causes eosinophilic meningitis disease commonly found in Southern East Asia and the Pacific Islands.[37] In one study, the effects of TSII-A (*Tanshinone* IIA) and *Cryptotanshinone* (CPT) with Albendazole on ocular nerve inflammation caused by *Angiostrongylus cantonensis* infection were evaluated in mice. The results showed the suitability of Albendazole in combination with TSI-E in the treatment of the optic nerve inflammation caused by *Angiostrongylus cantonensis*.[38]

The use of herbs for *Onchocerca ochengi*

Onchocerca ochengi is a bovine Filariasis parasite found in

West Africa as Cameroon. It is closely related to a human parasite called *Onchocerca volvulus*.[39] Studies by Ndjonka *et al.* showed antiparasitic activities of aqueous extracts of *Annona senegalensis* and *Euphorbia hirtam* and ethanolic extracts of *Parquetina nigrescens, Khaya senegalensis*, and *Anogeissus leiocarpus* with an LC50 concentration in a range of 0.08-0.55 mg/mL for *Onchocerca ochengi* worm. Based on this study, *Euphorbia hirta, Annona senegalensis, Khaya senegalensis,* and *Anogeissus leiocarpus* extracts can be suitable alternatives for worm infections.[40]

The use of herbs for *Ascaridia galli*

Ascaridia galli is one of the *Ascaridia* genus nematodes that live in poultry intestines and sometimes causes accidental closure of the intestine and Ascariasis in poultry.[41] In a study by Bazh and El-Bahy, a concentration of 100 mg/mL of ginger (*zingiber officinale*) and turmeric (*curcuma longa*) in 48 hours in an in vitro environment causes the death of *Ascaridia galli* worms in an in vivo environment, there was lower mortality. Also, in all concentrations, ginger caused more mortality than turmeric.[11]

Herbs' anthelmintic effect for *Toxocara vitulorum*

Toxocara vitulorum is the largest parasite, and its female species are up to 30 cm long. This parasite that lives in the intestine of cattle and buffalo calves, its spread is currently global, and often comes from tropical and subtropical areas, is one of the most important parasites of newborn calves.[42] In one study, using the methanolic extract of *Balanites aegyptiaca* fruit at a concentration of 240 mg/mL showed 100% inhibitory activity on *Toxocara vitulorum* egg growth.[43]

The use of herbs in *Trichinella spiralis*

An adult *Trichinella spiralis* is 4-6 cm long with a thick posterior end. Its anterior end suddenly narrows and forms as a thin and long wire embedded in the mucosa. *Trichinella spiralis* is the most important cause of human infections.[44] A study by Shalaby *et al.* showed that within five days, the methanolic extract of *Balanites aegyptiaca* with a concentration of 1000 mg/mL per kg of body weight in Rat reduced migration and death of larvae for 61/7% and, 81/7% respectively.[45]

The use of herbs for *Hymenolepis diminuta*

Hymenolepis diminuta that is also known as Tap worm rat (Rat), is the cause of Hymenolepiasis. Unlike *Hymenolepis nana*, this worm uses insects as mediator hosts for transmitting to infect humans.[46] Also, in a study by Yadav and Nath, the *Cynodon dactylon* extract had anthelmintic properties. A concentration of 40 mg/mL of the *Cynodon dactylon* extract caused paralysis and death of worms at hours 4/12 ± 0/55 and 5.16±0.32, respectively. Also, the treatment of rats by a dose of 800 mg/mL/kg for five days caused a reduction of 77.64% and 79.00% in the number of eggs per gram of feces and the worm load, respectively, after the treatment with *Cynodon dactylon*.[47]

The use of herbs for worms of the *Fasciolidae* family

These worms are large leaf-shaped flukes. The cone-shaped anterior end and the anterior balloon are located at the end of the cone. The abdomen balloon is at the level of the so-called shoulders of the fluke. There are three main genera, including *Fasciola*, *Fascioloide*s, and *Fasciolopsis*, in this family that often cause severe damage to their host's liver and intestines.[48] The ethanolic extract of *Alpinia nigra* in a 20 mg/mL concentration at hour 2.14±0.48 caused worm paralysis; While at hour 3.94 ± 0.23 caused the death of *Fasciolopsis buski* worms. In the control group, worms' physical activities continued until hour 21.05±0.22.[49] A study on *Fasciola hepatica* worm showed that the extract of *Lantana camara, Cajanus cajan,* and *Piper auritum* at a 50 mg/mL concentration caused 100% death worms. Whereas extracts of *Bocconia frutescens* and *Artemisia Mexicana* plants at a 125 mg/mL concentration caused 100% death of worms.[50] Research by Roy and Swargiary discussed about the role of *Fasciolopsis buski* in changing enzymes at *Alpinia nigra* tegument. Accordingly, by the effect of *Alpinia nigra* extract, the overall activity of Acid phosphatase (ATPase), Adenosine triphosphatase (ATPase), and Alkaline phosphatase (AlkPase) enzymes decreased because these enzymes have an important role in parasite survival by digesting and absorbing the nutrients.[51] Using Soybean extract reduces liver lesions because of the presence of *Fasciola gigantica* and the amount of 3-cell caspase of the liver, and on the other hand, caused induced apoptosis in the parasite DNA.[52]

The use of herbs for the *Schistosomatidae* family's

This family is located in the gastrointestinal tract and bladder's blood vessels. Schistosomiasis is an acute and chronic disease caused by *blood trematodes* of the genus *Schistosoma*. About 206 million people need preventive treatments to reduce the infection and prevent death from schistosomiasis.[53] In one study, different concentrations of Allicin caused morphological changes in *Schistosoma mansoni* in a way that a concentration of 10 mg/mL led to changes in small bumps and a reduction in the surface of the worm and at higher concentrations increased damaging the tegument, including vesicles and ulcers.[54] A study by Matos-Rocha *et al.* discussed the role of *Mentha x villosa Huds* Essential Oil (MVEO) against *Schistosoma mansoni* worms. MVEO at a concentration of 500 µg/mL caused the death of all worms within 24 hours, and examining it by SEM showed bubble-like lesions formed around the body of the worm and erosion in small bumps in some areas of the abdomen. Also, by studying using TEM, changes were observed in integument and vesiculation in the syncytial matrix region.[55] Using the *Clerodendrum umbellatum* extract in mice infected by *Schistosoma mansoni* significantly reduced the number of eggs excreted from mice; In a way that the amount of excreted eggs in treated mice with a concentration of 80 mg/kg and 160 mg/kg decreased by a rate of 75.48% and 85.14%, respectively.[56]

Herbs' use for the *Paramphistomatidae* family's

The adult *Paramphistomum* worm often exists in the ruminant pre-stomachs. Although, there is a species found in the intestines of ruminants, pigs, and dogs, which sometimes causes intestinal inflammation with edema, bleeding, and wounds.[57] In one study, the methanolic extract of *Bombax malabaricus* at a concentration of 100 mg/mL at minutes 22.17±0.48 caused the death of *Paramphistomum explanandum* worms, and at minutes 18.50±0.62 caused worm paralysis.[58] The *Balanites aegyptiaca* (BAE) fruit extract at a 200 µg/mL concentration caused severe damage to the *Paramphistomum microbothrium* tegument and the deformation of both suckers of the worm.[59]

Conclusions

Nearly all the plants in this review showed promising anthelmintic effects, mainly *in vitro* studies also plant medicines are thought to be good sources for the development of effective

anthelmintic agents. This work as well mentioned that there is a lack of studies on the effect of chemical constituents isolated from plants against helminth infections. Therefore, it is necessary to look for further effective anthelmintic drugs with minimum side effects.

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