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Anthelmintic activity of plants against gastrointestinal nematodes of goats: a review

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Review

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Abstract

The gastrointestinal nematodes (GIN) stand out as an important cause of disease in small ruminant, especially on goat farm. Widespread resistance to synthetic anthelminthics has stimulated the research for alternative strategies of parasite control, including the use of medicinal plants. The present work summarizes the *in vitro* and *in vivo* studies of plants with activity against GIN of goats, focusing on the description of chemical constituents related to this effect. This review retrieved 56 scientific articles from 2008 to 2018 describing more than 100 different plant species. The most frequently investigated family was Fabaceae (30.7%). Most *in vitro* studies on the activity of plant extracts and fractions were carried out with of free-living stages nematodes. *In vivo* studies were conducted mainly with the use of plants in animal feed and generally showed lower effectiveness compared to *in vitro* assays. The main plant secondary metabolites associated with anthelmintic effect are condensed tannins, saponin and flavonoids. However, the studies with compounds isolated from plants and elucidation of their mechanisms of action are scarce. Herbal medicines are thought to be promising sources for the development of effective anthelmintic agents.

Introduction

Gastrointestinal Nematodes (GIN) are an important cause of disease in small ruminant production worldwide, especially in tropical and subtropical countries. These parasites are responsible for substantial losses in productivity and can lead to mortalities and clinicopathological changes (Cantacessi *et al.*, 2012; Roeber *et al.*, 2013).

Goats and sheep are infected with the same GIN species, mainly *Haemonchus contortus*, *Trichostrongylus axei, Teladorsagia circumcincta* (abomasum), *T. colubriformis*, *Strongyloides papillosus, Nematodirus* spp. (small intestine), *Oesophagostomum columbianum* and *O. venulosum* (large intestine) (Hoste *et al.*, 2010; Bentounsi *et al.*, 2012; Moreno-Gonzalo *et al.*, 2013*a*). The nematode of major concern is *H. contortus*, a highly pathogenic parasite, because its blood-sucking feeding habits cause anemia, submandibular edema and lethargy. These infections promoted decrease in milk production, reduction of growth, weight loss, diarrhea, reproductive disorders and changes in carcass quality. In cases of massive infections, high mortality rates are observed (Molento *et al.*, 2011; Cantacessi *et al.*, 2012).

Goats are more susceptible to GIN probably due to a deficiency in the immune mechanism of parasite expulsion. Moreover, they metabolize anthelmintic drugs faster than do sheep, reducing the efficacy of anthelmintics when they are treated with the same dose recommended for sheep (Hoste *et al.*, 2010).

The most common method used to control GIN is the repeated use of synthetic anthelmintics. The main anthelmintic drugs used belong to the groups of benzimidazoles, imidazothiazoles, macrocyclic lactones (Hoste and Torres-Acosta, 2011), monepantel and derquantel (Kaminsky *et al.*, 2011). There are some disadvantages, such as the development of resistant populations, high cost, risk of environmental pollution and reduction of animal production due to low effectiveness (Adamu *et al.*, 2013). Drug inefficacy can be associated with many factors, such as incorrectly or badly managed/inadequately stored drug, dose level, inaccurately calculated weight and differences among animal species in pharmacokinetics (Torres-Acosta and Hoste, 2008).

Anthelminthic treatments are usually less effective in goats and could contribute to the nematode resistance. The goats are more susceptible than are sheep to gastrointestinal nematode infections with a higher production of worm eggs and elevated number of adult parasites in the gastrointestinal tract. These factors show that goats can be responsible for the dissemination of worm eggs from resistant nematodes in populations of small ruminants (Torina *et al.*, 2004).

In this context, the investigation of the antiparasitic activity of natural bioproducts can contribute to the development of alternative treatments and the reduction of the dependence on conventional chemotherapy (Santos *et al.*, 2017). The interest in their anti-parasitic properties

is increasing as illustrated by several reviews concerning ethnoveterinary medicine in different continents (Hounzangbe-Adote *et al.*, 2005; De Medeiros *et al.*, 2018).

The scientific validation of plants with antiparasitic activity requires the conduction of *in vitro* and *in vivo* studies to determine its effectiveness. Several *in vitro* tests were used to screen plants with anthelmintic activity of plants at different stages of the parasite, such as egg hatch assay (EHA), larval development assay (LDA), larval feeding inhibition assay (LFIA), larval migration inhibition assay (LMIA), larval exsheathment inhibition assay (LEIA) and adult motility inhibition assay (AMIA). Some assays were developed for *in vitro* drug screening or drug resistance testing of parasitic stages (Borges and Borges, 2016).

The adult motility inhibition assay (AMIA) is the only *in vitro* test to evaluate the anthelmintic effects on the parasitic life stage of the nematode (adult worm), which is the target of synthetic anthelmintic drugs. However, this test presents some limitations as the need to euthanize an animal infected with GIN and the maintenance of nematodes in a CO_2 incubator (short time of parasite viability) (Hounzangbe-Adote *et al.*, 2005; Andre *et al.*, 2016).

The *in vitro* tests are characterized by low cost, rapid collection, good sensitivity, repeatability and their use of free-living stages (eggs, first- and third-stage larvae) and adult nematodes species. However, they are not able to evaluate host factors since the substances are applied directly on the parasite (O'Grady and Kotze, 2004; Borges and Borges, 2016).

The *in vivo* evaluation of anthelmintic efficacy is performed by the fecal egg count reduction test (FECRT) or controlled test. The FECRT provides an estimate of the reduction in the excretion of eggs after treatment, while in the controlled test the effectiveness is assessed by comparing the parasite burdens in the treated groups compared to the control group. The controlled test is the most reliable method, but also the most expensive analysis in terms of labor requirements and animal usage (Taylor *et al.*, 2002).

Most studies on the anthelmintic activity of plants in small ruminants were performed in sheep. However, the results obtained from studies with this species cannot be extrapolated to goats because of immunological, physiological and behavioral differences between sheep and goats (Torres-Acosta *et al.*, 2004). The aim of this study is to provide an overview of the anthelmintic properties of the plants against GIN of goats, as well as to identify bioactive constituents related to this effect.

Methods

For the article collection, we used the databases PubMed (database of the National Library of Medicine of the United States of America) and Science Direct, the Elsevier scientific literature platform belonging to the RELX group. We considered all original articles published between 2008 and 2018 and that investigated the activity of plants and their derivatives in the treatment against GIN of goats. The search strategy was based on three descriptors: plants, gastrointestinal nematodes and goats.

The abstracts of the articles were analyzed and after the initial screening, all relevant studies were recovered in full-text and evaluated. Only studies investigating plant extracts, its fractions and isolated compounds against GIN of goats were considered for potential inclusion in the review. *In vitro* and *in vivo* studies were included. The methods of exclusion were based on the following criteria: studies in small ruminants without specifying the animal species, studies testing synthetic or commercial substances and studies that were not research articles (i.e. review articles, encyclopedia, correspondence and book chapters).

Results

337 articles were recovered in the two databases. After screening, 56 studies that presented the research object were found, out of which 17 were referred on the PubMed platform, 26 on the Science Direct platform and 13 on both platforms. These duplicate studies were compared through authors, title, year and journal of publication. Figure 1 shows the Flowchart of the general characteristics in the selection process to recover these articles.

The years from 2012 and 2013 presented most scientific productions, with 8 publications each. As for the countries responsible for the publications, Brazil was the country with the largest number ($n = 14$), followed by the United States of America ($n = 10$) and Spain ($n = 6$).

Table 1 shows 28 *in vitro* studies on the effects of plants against the GIN of goats. 32 families and 78 plant species were evaluated in *in vitro* studies. While Table 2 shows 30 *in vivo* studies, we identified the citation of 41 plants belonging to 18 families. Only two papers presented *in vitro* and *in vivo* tests in the same study. Considering the number of articles analyzed, the most frequently investigated family was Fabaceae (46.42%), followed by Ericaceae (14.29%), Asteraceae (7.14%) and Rhamnaceae (5.35%). In this review, the *Lespedeza cuneata* (Fabaceae) and *Calluna vulgaris* (Ericaceae) were the most studied species (6 articles for each species).

The *in vitro* studies were carried out mainly with stages of free-living *Haemonchus contortus* (64.2%) and *Thrichostrongylus* (35.7%) spp. Many plants exhibited *in vitro* anthelmintic activity at a lower concentration (EC_{50} <1.0 mg mL^{-1}), such as *Calluna vulgaris, Erica cinerea, E. umbellata* (Ericaceae), *Acacia nilotica, A. raddiana* (Fabaceae), *Persea Americana* (Lauraceae) and *Digitaria insularis* (Poaceae). The ethyl acetate extracts of *C. vulgaris* and *E. cinerea* were active on different stages of GIN (egg, larvae L_3 and adult parasite) (Table 1).

The *in vivo* studies were characterized by the oral administration of the leaves (fresh, hay, meal), aqueous extract and oil of plants to goats infected naturally or experimentally with GIN. The duration of treatment ranged from 01 to 189 days. The efficacy parameter frequently evaluated was the reduction in EPG (90%), followed by recovery of adult parasites (16.7%).

The main plant secondary metabolites associated with anthelmintic effect are condensed tannins (68%), saponins (12.5%) and flavonoids (8.9%). This review showed that the evaluation of anthelmintic activity of isolated compounds on goat's parasites is scarce. Only two studies *in vitro* (7.4%) used commercial substances that are found in plants: the flavonoids (quercetin, rutin and epicatechin) and the saponins (escin and digitonin).

Discussion

In vitro *studies of the anthelmintic activity of plants*

Plants stand out as an important source of new candidates for anthelmintic drugs. Several *in vitro* tests, as egg hatch and larval migration, motility and exsheathment assays, have been used to identify plants with effect against the GIN of goats.

Studies show that many plants evaluated bear anthelmintic properties against different abomasal and small intestine nematodes. In this review, antiparasitic effects of plants vary depending on the plant species, stage, the nematode species and the parasitic stage. *Erica cinera* was more active against eggs and L_3 of *T. columbriformis* than to inhibit the egg hatching and larvae exsheathment of abomasal parasites (*H. contortus* and *T. circumcinta*) (Moreno-Gonzalo *et al.*, 2013*a*, 2013*b*). The *Agave sisalana* and *Moringa oleifera* has greater ovicidal effect while *Acacia nilotica* and *A. raddiana* are more active against L_3 of GIN (Botura *et al.*, 2013; Zabré *et al.*, 2017; De Medeiros *et al.*, 2018). These

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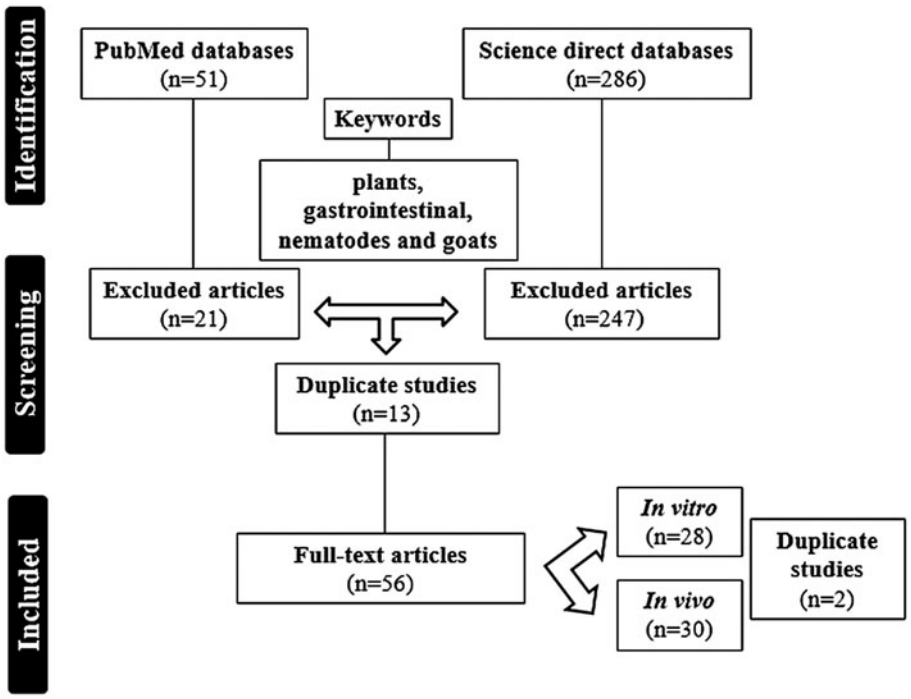

Fig. 1. Flowchart of the general characteristics for selection process of the articles.

variations can be related with differences in various enzymatic constituents and membrane structures of the species and nematodes' life stages. Plant secondary metabolites can act by means of different mechanisms such as: inhibition of egg hatching enzymes, competition with membrane receptors and binding to proteins in the membrane (Chan-Pérez *et al.*, 2016).

The use of standardized *in vitro* methods is essential for the assessment of the efficacy of plant products, particularly the determination of EC_{50} and EC_{90} (effective concentration 50% and 90%), which allows the comparison of activities of different plants (Borges and Borges, 2016). Adamu *et al.* (2013) established that a plant extract with EC_{50} below 6 mg mL^{-1} shows great anthelmintic potential. Considering this parameter, many plants recorded in this review have a promising antiparasitic effect. However, we found variations in the indices of efficacy for the same plant species, such as *Agave sisalana, Pistacia lentiscus, Calluna vulgaris* and *Erica umbellata*. This finding may be related to the type of preparation of the plant, stage and species of the parasite, contact and the time of exposure of the parasite to the vegetal product (Hernández-Villegas *et al.*, 2011). Some factors should be observed to avoid false positive or false negative results such as operator experience, choice of solvents, packaging and solubilization of plant products, quality of water and pH of the solutions used in the tests (Borges and Borges, 2016).

Variations in collection and preparation procedures of plant materials can interfere in the reproducibility of assays. Hence, chemical characterization of herbal products may be useful for the scientific validation of their antiparasitic activity. Phytochemical analyses using methods of mass spectrometry (liquid-chromatography mass spectrometry and gas-chromatography mass spectrometry) can aid in identifying the bioactive compounds found in plants (Hoste *et al.*, 2006).

In this review, it can be seen that anthelmintic activity of plants was evaluated mainly against stages of free-living nematodes (egg and larvae L_3). Although the synthetic anthelmintic drugs act on the parasitic stages, the action on the stages of free-living nematodes can be useful for the control of helminths. Ovicidal action of plants can prevent parasitic development of the infective stage and reduce the pasture contamination (Silveira *et al.*, 2012). The evaluation of the activity of plant products against different stages of parasites is necessary, since the action of phytocompounds can be different depending on the phases of the parasite's development (Borges and Borges, 2016).

The anthelmintic activity of medicinal plants has been related to secondary metabolites. The major classes of bioactive metabolites are flavonoids, alkaloids, coumarins, lignoids, triterpenes, saponins, polyphenols and tannins. The tannins are the most studied class of natural products for nematode control in small ruminants (Hoste and Torres-Acosta, 2011). The anthelmintic effect of tannins is attributed to its ability to bind to the proteins present in the cuticle, oral cavity, esophagus, cloaca and vulva of the nematodes, changing its physical and chemical properties. Another possibility is related to an indirect action of these compounds, which can enhance the host immune response due to its binding with proteins of the diet, protecting these substances from ruminal degradation and thereby increasing protein availability in the small intestine (Hoste *et al.*, 2006).

Several studies have showed the anthelmintic potential of the plants rich in condensed tannins. *In vitro* evaluations demonstrated effects of tanniferous plant extracts on the larval migration, larval artificial exsheathment, adult motility inhibition and egg hatching of *H. contortus* (Alonso-Díaz *et al.*, 2008; Moreno-Gonzalo *et al.*, 2013*a*; Naumann *et al.*, 2014). The use of polyvinylpolypyrrolidone (PVPP), an inhibitor of tannins, confirmed that this metabolite is responsible for the anthelmintic activity of the tanniferous plants (Alonso-Díaz *et al.*, 2008). The effect of larval exsheathment may be related to the presence of proline and hydroxiproline-rich proteins in the nematode larval sheath, cuticle and exsheathing fluid and these substances have high affinity for tannins. The exsheathment process is an important step, which is the transition from the free stage to the parasitic stage, allowing the larvae infection of the host (Alonso-Díaz *et al.*, 2011).

In vitro study with *Lysiloma latisiliquum* and *Onobrychis viciifolia*, rich in tannins, showed that the exposure of *H. contortus* (adult stage) to the extract acetone: water (70:30) of these plants led to changes in parasite structure: longitudinal and transversal folds and thicker cuticular ridges, aggregate material in the regions of the buccal capsule and anus or vulva. Alterations in cuticular structure can interfere with the movement of nematodes

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Table 1. *In vitro* studies on the effects of plants against gastrointestinal nematodes

Family	Species	Part(s) used	Preparation	Parasite	Concentration (mg mL^{-1})	Active constituent	Results (EC_{50}, IC_{50}: mg mL^{-1})	Reference
Agavaceae	*Agave sisalana*	Waste	Juice	Gastrointestinal nematodes	39.3–146.3	Saponins	Reduction of larval counts (coproculture assay): >95%	Domingues et al. (2010)
	Agave sisalana	waste	A, EA, SF and FF	Gastrointestinal nematodes	0.02–10	Flavonoids and saponins	EHI: IC_{50}: 4.7 (A), 0.1 (EA) and 0.05 (FF) LMI (%): 33.3 (A), 50.3 (EA) and 64 (SF)	Botura *et al.* (2013)
Anacardiaceae	*Pistacia lentiscus*	L	E (70%); E (100%); A (infusion)	*Teladorsagia circumcincta, Trichostrongylus colubriformis* and *Chabertia ovina*	0.0024–0.012	Phenolics (catechin, flavonolglucosides, galloyl derivatives)	LEI: E (70%): 18.3–0.9 (semi log slope) E (100%) and A: Low larvicidal activity	Azaizeh *et al.* (2013)
	Pistacia lentiscus	L	E (70%)	*T. circumcinta* and *T.colubriformis*	0.6–2.4	Phenolics (tannins, gallic acid)	LEI: 0–25%	Azaizeh *et al.* (2015)
Asteraceae	*Cichorium intybus* (two cultivars: Puna and Forage Feast)	L	ESL	*Haemonchus contortus*	1.67–10	Sesquiterpenes lactones (8-deoxylactucin)	EHI: EC_{50}: 2.6 (Puna) and 6.4 (Forage Feast)	Foster *et al.* (2011)
	Inula viscosa	L	E (70%)	*T. circumcinta* and *T. colubriformis*	0.6–2.4	Phenolics (tannins, gallic acid)	LEI: 23–54%	Azaizeh *et al.* (2015)
Cupressaceae	*Juniperus pinchotii*	L	Rumen fluid with dried plant, fresh plant, oil	*H. contortus*	0.0001–0.006	Terpenoids and condensed tannins	LMI: Dried and Fresh Plant: 40–60% Oil >60%	Armstrong *et al.* (2013)
Ericaceae	*Calluna vulgaris*	AP	Ac (70%)	*T. circumcinta* and *H. contortus*	0.075–1.2	Phenols (condensed tannins)	EHI: 20% (*T. circumcincta* and *H. contortus*). LEI: EC_{50} = 0.61 (*T. circumcincta)* and 0.19 (*H. contortus).* AMI (*T. circumcinta*): 90% (+40 h exposure)	Moreno-Gonzalo *et al.* (2013*a*)
	Calluna vulgaris	AP	Ac (70%), CTF	*T. colubriformis*	0.075–1.2	Phenols (condensed tannins)	EHI: EC_{50} = 0.52 (Ac 70%) LEI: EC_{50} = 0.57 (Ac 70%), 0.07 (CTF) AMI (*T.colubriformis*): 90% (+90 h exposure) (Ac 70%)	Moreno-Gonzalo *et al.* (2013*b*)
	Erica cinerea	AP	Ac (70%)	*T. circumcinta* and *H. contortus*	0.075–1.2	Phenols (condensed tannins)	EHI (%): 45 (*T. circumcincta*) and 30 (*H. contortus*) LEI: EC_{50} = 0.21 (*T. circumcincta*) and 0.22 (*H. contortus*) AMI (*T. circumcinta*): 75% (+40 h exposure)	Moreno-Gonzalo *et al.* (2013*a*)
	Erica cinerea	AP	Ac (70%), CTF	*T. colubriformis*	0.075–1.2	Phenols (condensed tannins)	EHI: EC_{50} = 0.34 (Ac 70%) LEI: EC_{50} < 0.15 (Ac 70%), 0.108 (CTF) AMI (*T.colubriformis*): 70% (+90 h exposure)(Ac 70%)	Moreno-Gonzalo *et al.* (2013*b*)
	Erica umbellata	AP	Ac (70%)	*T. circumcinta* and *H. contortus*	0.075–1.2	Phenols (condensed tannins)	EHI: 10–20% (*T. circumcincta*) and 10–30% (*H. contortus*). LEI: EC_{50} = 0.77 (*T. circumcincta)* and 0.179 (*H. contortus).* AMI (*T. circumcinta*): >90% (+ 40 h exposure)	Moreno-Gonzalo *et al.* (2013*a*)

	Erica umbellata	AP	Ac (70%), CTF	*T.colubriformis*	0.075–1.2	Phenols (condensed tannins)	EHI: EC_{50} = 0.121 (Ac 70%) LEI: EC_{50} < 150 (Ac 70%) AMI (*T.colubriformis*): 70% (+ 70 h exposure) (Ac 70%)	Moreno-Gonzalo *et al.* (2013*b*)
	Association of *C. vulgaris, E. cinerea, E. umbellata*	AP	Ac (70%)	*T. circumcinta* and *H. contortus*	0.075–1.2	Phenols (condensed tannins)	EHI: 80% (*T. circumcincta*) and 10-15% (*H. contortus*) LEI: EC_{50} = 0.696 (*T. circumcincta*) and 0.253 *(H. contortus*) AMI (*T. circumcinta*): 100% (+ 20 h exposure)	Moreno-Gonzalo *et al.* (2013*a*)
	Association of *C. vulgaris, E. cinerea, E. umbellata)*	AP	Ac (70%), CTF.	*T. colubriformis*	0.075–1.2	Phenols (condensed tannins)	EHI: EC_{50} = 0.791 (Ac 70%) LEI: EC_{50} < 150 (Ac 70%), 0.39 (CTF) AMI (*T. colubriformis*): 100% (+ 70 h exposure) (Ac 70%)	Moreno-Gonzalo *et al.* (2013*b*)
Euphorbiaceae	*Manihot esculenta*	L	M (80%)	*T. circumcincta*	3.1–50	–	M (50 mg mL^{-1}): EHI: 43.97–45.67% LDI: 97.11–98.96% LMI: 39.44–44.31%	Al-Rofaai *et al.* (2012*a*)
	Manihot esculenta	L	M (80%)	*T. colubriformis*	3.1–50	Tannin condensed	EHI: LC_{50} = 50.08–55.67 Larvicidal activity: $LC_{50:}$ L_1: 16.07–16.89 L_3: 81.40 (susceptible) and 101.80 (resistant)	Al-Rofaai *et al.* (2012*b*)
Fabaceae	*Acacia angustissima var hirta* (STX)	L.	Rumen fluid	*H. contortus*	–	Condensed tannins	LMI < 45%	Naumann *et al.* (2014)
	Acacia angustissima var hirta (STP5)	L.	Rumen fluid	*H. contortus*	–	Condensed tannins	LMI < 45%	Naumann *et al.* (2014)
	Acacia nilotica	L	A and Ac	*H. contortus*	0.15–5.0	Phenolics (condensed tannins)	EHI: IC_{50} > 5 (A and Ac) LEI: IC_{50} = 0.195 (A) and 0.224 (Ac)	Zabré *et* al. (2017)
	Acacia pennatula	L	Ac:A	*H. contortus*	1.2	Tannins	LMI: 43% LEI: 97%	Alonso-Diaz *et al.* (2008)
	Acacia raddiana	L	A and Ac	*H. contortus*	0.15–5.0	Phenolics (condensed tannins)	EHI: IC_{50}: 1.36 (A) and 0.68 (Ac) LEI: IC_{50}: 0.331 (A) and 0.207 (Ac)	Zabré *et* al. (2017)
	Arachis glabrata	L.	Rumen fluid	*H. contortus*	–	Condensed tannins	LMI < 45%	Naumann *et al.* (2014)
	Desmanthus illinoensis	L.	Rumen fluid	*H. contortus*	–	Condensed tannins	LMI < 45%	Naumann *et al.* (2014)
	Hedysarum carnosum	WP	Ac (70%)	*H. contortus*	0.15–1.2	Phenols (condensed tannins)	LEI: 25.67–98.44%	Aissa *et al.* (2016)
	Lespedeza cuneata	L.	Rumen fluid	*H. contortus*	–	Condensed tannins	LMI < 45%	Naumann *et al.* (2014)
	Lespedeza stuevei	L.	Rumen fluid	*H. contortus*	–	Condensed tannins	LMI: 60–65%	Naumann *et al.* (2014)
	Leucaena leucocephala	L	Ac:A	*H. contortus*	1.2	Tannins	LMI: 44% LEI: 89%	Alonso-Diaz *et al.* (2008)

(*Continued*)

Table 1. (*Continued.*)

Family	Species	Part(s) used	Preparation	Parasite	Concentration (mg mL^{-1})	Active constituent	Results (EC_{50}, IC_{50}: mg mL^{-1})	Reference
	Leucaena retusa Benth.	L	Rumen fluid	*H. contortus*	–	Condensed tannins	LMI: 65.4%	Naumann *et al.* (2014)
	Lysiloma latisiliquum	L	Ac:A	*H. contortus*	1.2	Tannins	LMI: 33% LEI: 95%	Alonso-Diaz *et al.* (2008)
	L. latisiliquum *Onobrychis viciifolia*	L	AC:A (70:30)	*H.contortus*	1.2	Condensed tannins	Structural changes in adult parasite: longitudinal and transversal folds; thicker cuticular ridges, material aggregates (buccal capsule and/or vulva or anus)	Martínez-Ortíz-de-Montellano *et al.* (2013)
	O. viciifolia	Hay	Ac (70%)	*T. circumcincta* *H. contortus*	0.3–1.2	Condensed tannins	LEI (%): 47.9 (*T. circumcincta*) 87.17 (*H. contortus*)	Brunet *et al.* (2008*a*)
	O. viciifolia	Hay	A	*H. contortus* and *T. colubriformis*,	1.2	Condensed tannins	No significant structural changes were detected.	Brunet *et al.* (2011)
	Piscidia piscipula	L	Ac:A	*H. contortus*	1.2	Tannins	LEI: 95%	Alonso-Diaz *et al.* (2008)
	Prosopis juliflora	Pods	EA and AF	*Haemonchus spp.* *Trichostrongylus spp.* and *Oesophagostomum spp.*	0.79–4.0	Alkaloids	EHI: IC_{50} = 1.9; IC_{90}: 2.9 (EA) IC_{50} = 1.1; IC_{90}: 1.43 (AF) No activity on larval migration and motility	Lima *et al.* (2017)
	Bowdichia virgilioides	R	Flavonoids isolated	*Haemonchus spp.* *Oesophagostomum spp.* and *Trichostrongylus spp.*	1	Isocordoin and cordoin + isocordoin	Low ovicidal and larvicidal activity	Santos *et al.* (2018)
Grossulariaceae	*Ribes nigrum*	L		*H. contortus*	Fr: 0.0375–0.6 quercetin and luteolin: 30 and 60 µM	Condensed Tannins	LEI: EC_{50} Fr: 0.277 Fr + Quercetin: 0.137 (60 µM), 0.164 (30 µM) Fr + luteolin: 0.0312 (60 µM), 0.170 (30 µM)	Klongsiriwet *et al.* (2015)
	Ribes rubrum	L		*H. contortus*	Fr: 0.0375–0.6 quercetin and luteolin: 30 and 60 µM	Condensed Tannins	LEI: EC_{50} Fr: 0.126 Fr + Quercetin: 0.0788 (60 µM)	Klongsiriwet *et al.* (2015)
Lauraceae	*Persea americana*	S	E and H	*H. contortus*	1	condensed tannins, flavonoids	LMI: E: Ec_{50} = 0.036 (Dried) and 0.147 (Fresh) H: Ec_{50} = 0.077 (Dried) and 0.801 (Fresh)	Soldera-Silva *et al.* (2018)
Malvaceae	*Tilia spp.*	Fl	CTF	*H. contortus*	Fr: 0.0375–0.6 quercetin and luteolin: 30 and 60 µM	Condensed Tannins	LEI: EC_{50} Fr: 0.356 Fr + Quercetin: 0.0624 (60 µM), 0.156 (30 µM) Fr + luteolin: <0.0375 (60 µM), 0.0759 (30 µM)	Klongsiriwet *et al.* (2015)

Meliaceae	*Azadirachta indica*	L	H, C, EA and M (80%)	*T. circumcincta*	3.1 to 50	Tannin	M (80%): –EHI: IC_{50} = 44.2 (susceptible strain) IC_{50} = 47.7 (resistant strain) –LDI: IC_{50} = 7.15 (susceptible strain) IC_{50} = 7.32 (resistant strain) –LMI: IC_{50} = 24.91 (susceptible strain) IC_{50} = 35.03 (resistant strain) H,C and EA: Low ovicidal and larvicidal activity	Al-Rofaai *et al.* (2012*b*)
Moringaceae	*Moringa oleifera*	S	A	*Strongyloides genera, Oesophagostomum spp., Haemonchus spp.* and *Trichostrongylus spp.*	1.95–250	Lectin	EHI: 40,4% LEI (L_1 and L_3): EC_{50} = 0.078	De Medeiros *et al.* (2018)
	Moringa oleifera	S	A and E	*H. contortus*	0.95–15.6	Tannins, saponins, Alkaloids, flavonoids and terpenoids	EHI: IC_{50} = 2.91 (E); 3.83 (A) LEI: $IC_{5\ 0}$ = 6.96 (E); 4.12 (A)	Cabardo and Portugaliza (2017)
Myrtaceae	*Eucalyptus staigeriana*	L	EO	*H. contortus*	0.08–5.4	Limonene and citral	EHI: IC_{50} = 0.324 LDI: IC_{50} = 1.7	Macedo *et al.* (2010)
Oleaceae	*Phillyrea latifolia*	L	E (70%); E (100%); A (infusion)	*T. circumcincta*, *T. colubriformis and Chabertia ovina*	0.012–0.12	Phenolics (catechin, flavonolglucosides, galloyl derivatives)	LEI: E (70%): 21.1–1.4 (semi log slope) E (100%) and A: Low larvicidal activity	Azaizeh *et al.* (2013)
	Phillyrea latifolia	L	E (70%)	*T. circumcinta* and *T. colubriformis*	0.6–2.4	Phenolics (tannins, gallic acid)	LEI: 47–57%	Azaizeh *et al.* (2015)
Poaceae	*Digitaria insularis*	L	Extracts (HE, EA, B and RH) Fractions of EA (FR1 to FR6)	*H. contortus*, *Oesophagostomum* spp. *Trichostrongylus* spp.	0.08–2.5	Flavones (tricin and diosmetin)	EHI: all extracts and FR2 and FR3 (>90%). EC_{50} = 0.7 (EA) EC_{50} = 0.27 (FR2) No activity on larval motility	Santos *et al.* (2017)
Rhamnaceae	*Zizyphus joazeiro*	B	H, EA, SF and BA	*H. contortus*, *Oesophagostomum* spp. and *Trichostrongylus* spp.	0.5–4.0	Saponins	EHI: H: 48%, BA: 17%; EC_{50} = 1.9 (EA) and 1.3 (SF) No activity on larval migration and motility	Gomes *et al.* (2016)
	Ziziphus jujuba	L	A	*H. contortus*	0.1–1.75	–	EHI: IC_{50} = 0.302, IC_{90} = 0.849 Adult assay: IC_{50} = 0.943, IC_{90} = 2.05	Preet and Tomar (2017)
Salicaceae	*Salix caprea*	L		*H. contortus*	Fr: 0.0375–0.6 quercetin and luteolin: 30 and 60 μM	Condensed Tannins	LEI: EC_{50} Fr: 0.394 Fr + Quercetin: 0.103 (60 μM)	Klongsiriwet *et al.* (2015)
Various families	Various species	L and P	E (70%)	*T. circumcinta* and *T. colubriformis*	0.125 to 1.0 mg mL^{-1}	Phenolics and tannins	LEI: 7–94%	Jamous *et al.* (2017)

Parts used: AP, Aerial Part; B, bark; L, leaf; Fl, Flower; Fr, Fruit; R, Root; S, Seed; ST, Stem; WP, Whole Plant.
Extracts: A, Aqueous; Ac, Acetone; EA, Ethyl Acetate; B, Butanol; C, Chloroform; D, Dichloromethane; E, Ethanol; HE, Hydroethanol; RH, Residual Hydroethanol; M, Methanol; H, hexane; EO, Essential Oil; ESL, Extract Rich in Sesquiterpene Lactones; CTF, Condensed Tannins Fraction; FGF, Flavonol Glycosides Fraction; SF, saponins fraction; FF, flavonoids fraction; AF, alkaloid-rich fraction; BA, betulinic acid; SA, Succinic acid.
Egg hatch inhibition (EHI), Larval development inhibition (LDI), Larval migration/motility inhibition (LMI), Larval exsheathment inhibition (LEI), Adult motility inhibition (AMI)

Table 2. *In vivo* studies on anthelmintic activity of plants in goats infected with gastrointestinal nematodes

Family	Species	Part used	Preparation	Treatment	Active constituent	Results	Reference
Agavaceae	*Agave sisalana*	Waste	Juice	0.92 g kg^{-1} during 4–8 days	Saponins	No effect in EPG and worm burn Reduction in FLC: 95%	Domingues *et al.* (2010)
	Agave sisalana	Waste	Aqueous extract	1.7 g kg^{-1} per 8 days	Saponins	Reduction of EPG (50.3%) No effect in worm burden	Botura *et al.* (2011)
Alliaceae	*Allium sativum*	Bu	Juice	40 mL or 3 bulbs $animal^{-1}$ per 7 days	–	No effect (EPG)	Burke *et al.* (2009*a*)
Anacardiaceae	*Pistacia lentiscus*	L	Fresh leaves	*Ad libitum* per 24 days	Condensed tannins	Reduction of EPG (low value)	Landau *et al.* (2010)
Asphodelaceae	*Aloe ferox* (Mill).	L	Extract powder	250 and 500 mg kg^{-1} (9 days)	Amino acids and saponins	Reduction of EPG (38.75–48.79%)	Maphosa and Masika (2012*a*)
Asteraceae	*Viguiera dentata*	L	Fresh Leaves	*Ad libitum* for 1 h daily/10 days	Condensed Tannins	Reduction of EPG (91.17%)	Ventura-Cordero *et* al. (2017)
Casuarinaceae	*Casuarina cunninghamiana*	L	Fresh	*Ad libitum* per 8 days	Polyphenols Tannins	Lower reduction of egg output and larvae recovered from faecal cultures No effect in worm burden	Moreno *et al.* (2012)
Ericaceae	*Calluna vulgaris* *Erica umbellata and E. cinerea*	L	Hay	30–40 g DM kg $BW^{-0.75}$ per day for 11 weaks	Condensed tannins	Preventive: Reduction of EPG (14%) Curative: Reduction of EPG (47–66%)	Moreno-Gonzalo *et al.* (2014)
	Erica spp. or Calluna vulgaris (heather)	L	Fresh Leaves	Twice per week (*ad libitum*)	Condensed tannins	No effect (EPG)	Osoro *et al.* (2009)
	Erica spp. or Calluna vulgaris (heather)	L	Fresh Leaves	0.5 kg $head^{-1}$ day^{-1}	Condensed tannins	Reduction of EPG (50.64%)	Celaya *et al.* (2010)
	Erica spp. or Calluna vulgaris (heather)	L	Hay	30 g DM kg $BW^{-0.75}$ per day for 3 weaks	Condensed tannins	Reduction of EPG (40–50%)	Moreno-Gonzalo *et al.* (2013*c*)
Euphorbiaceae	*Manihot esculenta*	L	Fresh and silage	*Ad libutum* (21 days)	–	Reduction of EPG: ∼42.13% (fresh) and ∼10.11 (silage)	Sokerya *et* al. (2009)
Fabaceae	*Acacia karroo*	L	Fresh leaves	200 g $head^{-1}$ day^{-1}	Polyphenols (condensed tannins)	Reduction of FLC (±80%) RAW: 90%.	Marume *et* al. (2012)
	Acacia mearnsii	B	Commercial extract	24 g $animal^{-1}$ per 27 weeks	Condensed tannins	Reduction of EPG (first half of the treatment) Worm burden: no change	Costa-Junior *et al.* (2014)
	Acacia nilotica	L	Fresh	*Ad libitum* per 8 days	Polyphenols	Lower reduction of egg output and larvae recovered from faecal cultures No effect in worm burden	Moreno *et al.* (2012)
	Bauhinia pulchella	L	Concentrate	180 mg kg^{-1} per 63 days	Condensed tannins	No significant reduction in EPG Reduction on worm egg hatchability	Lopes *et al.* (2016)
	Desmodium intortum	L	Chopped	350 g day^{-1} (98 days) 10 g PEG 6,000	Condensed tannins	Reduction of EPG (91.3%) compared to the group receiving PEG	Debela *et* al. (2012)
	Elephantorrhiza elephantina	R	Extract powder	250 mg kg^{-1} and 500 mg kg^{-1} (9 days)	Tannins	Reduction of EPG (22.22–64.19%)	Maphosa and Masika (2012*a*)

	Elephantorrhiza elephantina	R	Aqueous fractions	12.5 to 75 mg mL^{-1} dosed at 2 mL per 10 kg for 2 months	Condensed tannins	Reduction of EPG: 81.7 to 98.6%	Maphosa and Masika (2012*b*)
	Lespedeza cuneata	L	Leaf meal	75 and 95% SL leaf meal pellets and a commercial pellet, all fed at 0.91 kg $head^{-1}$ day^{-1} per 3 months	Condensed tannins	Reduction of EPG: 75–95%. RAW: 31-93.5% (*H. contortus*), 47% (at 95%SL) (*T. circumcincta*) (at 95%SL) 32.3% (*T. colubriformis*)	Gujja *et al.* (2013)
	Lespedeza cuneata	L	Hay	75% diet per 6 weeks	Condensed tannins	Reduction of EPG (91.9%) and the number of abomasal nematodes (74%)	Terrill *et al.* (2009)
	Lespedeza cuneata	L	Fresh Leaves	0.45 kg $head^{-1}$ d^{-1} (first 4 weeks), and 0.27 kg $head^{-1}$ d^{-1} (final 4 weeks)	Condensed tannin	Reduction of EPG (82.4%) RAW: 52%	Mechineni *et al.* (2014)
	Lespedeza cuneata	L	Leaf meal	Feeding: 90% leaf meal pellets (stored less than 6 months and 3 years)/28 days	Condensed tannins;	Reduction of EPG (66.2–79.2%)	Kommuru *et al.* (2014)
	Lespedeza cuneata	L	Pellets (75% *S. lespedeza*)	*Ad libitum* per 28 days	Condensed tannins	Reduction of EPG (58%) No effect in worm burden (abomasal) Cuticular surface damage in adult *H. contortus*	Kommuru *et al.* (2015)
	Leucaena leucocephala Mimosa bahamensis	L	Fresh Leaves	*Ad libitum* for 1 h daily per 10 days	Condensed tannins	Reduction of EPG (91.17%)	Ventura-Cordero *et* al. (2017)
	Lysiloma latisiliquum	L	Fresh leaves	28 days post infection: 800 g per 7 days	Tannin	Structural differences on the cuticle and a lesser extent the buccal capsule.	Martínez-Ortíz-de-Montellano *et al.* (2013)
	Lysiloma latisiliquum	L	Fresh leaves	10 g kg^{-1} for 6 days	Condensed tannins	RAW: *H. contortus* (57%), *T. colubriformis* (64.3%)	Brunet *et al.* (2008*b*)
	Mimosa caesalpiniifolia	L	leaf powder	64.3–128.7 mg of CT per kg BW per day (21 days)	Condensed Tannins	Reduction of EPG: 28.9 to 51.6% to 28.9% RAW: 57.7%	Brito *et al.* (2018)
	Onobrychis viciifolia	L	Hay	28 days post infection: *Ad libitum* per 7 days	Tannin	No significant structural changes were detected.	Martínez-Ortíz-de-Montellano *et al.* (2013)
	Quercus leucotricophora	L	Roughage	Feeding: 70% per 120 days	Condensed tannins	Reduction of EPG (± 80%)	Raju *et al.* (2015)
	Quercus semecarpifolia	L	Roughage	Feeding: *70%* per 120 days	Condensed tannins	Reduction of EPG (± 80%)	Raju *et al.* (2015)
	Sesbania sesban	L	Hay	220 g day^{-1} (98 days)	Condensed tannins	Reduction of EPG (52.6%)	Debela *et* al. (2012)
Lamiaceae	*Leonotis leonurus*	L	Extract powder	250 mg kg^{-1} and 500 mg kg^{-1} (9 days)	Alkaloids, saponins and tannins	Reduction of EPG (47.26–80.62%)	Maphosa and Masika (2012*a*)
Myrtaceae	*Eucalyptus staigeriana*	L	Essential oil	500 mg kg^{-1} (single dose)	Limonene and citral	Reduction of EPG (76.6%)	Macedo *et al.* (2010)
	Eucalyptus corymbia, Eucalyptus drepanophylla	L	Fresh	*Ad libitum* per 8 days	Polyphenols	Lower reduction of egg output and larvae recovered from faecal cultures No effect in worm burden	Moreno *et al.* (2012)
Phytolaccaceae	*Phytolacca icosandra*	L	Ethanolic extract	250 mg kg^{-1} per 2 days	Saponins, coumarins, flavonoids, steroids, terpenoids	Reduction of EPG (72%)	Hernández-Villegas *et* al. (2012)

(*Continued*)

Table 2. (*Continued.*)

Family	Species	Part used	Preparation	Treatment	Active constituent	Results	Reference
Poaceae	*Sorghum bicolor*	G	Grain	*Ad libitum* 14 × 10^{21} days	Condensed tannins	No effect in EPG	Whitley *et al.* (2009)
	Zea mays	G	Grain	Supplement 108: 108 g d^{-1} Supplement 1%: 1% BW Supplement 1.5%: 1.5% BW	–	Supplement 1.5%: reduction of EPG (55.57%) Supplement 108 and 1%: no effect in EPG	Gárate-Gallardo *et* al. (2015)
Polygonaceae	*Gymnopodium floribundum*	L	Fresh Leaves	*Ad libitum* for 1 h daily per 10 days	Condensed Tannin	Reduction of EPG (91.17%)	Ventura-Cordero *et* al. (2017)
Asteraceae, Alliaceae, Apiaceae, Juglandaceae	*Artemisia absinthium, Allium. sativum, Foeniculum vulgare, Juglans nigra and Stevia rebaudiana*	–	Dewormer formula	19 g once daily/3 days (repeated after 62 days)	–	No effect (EPG)	Burke *et al.* (2009*b*)
Cucurbitaceae, Asteraceae, Alliaceae, Apiaceae, Lamiaceae	*Curcubita pepo, A. vulgaris, A. sativum, F. vulgare, Hyssopus officinalis, Thymus vulgaris, and S. rebaudiana*	–	Dewormer formula	19 g dose daily per 7 days	–	No effect (EPG)	Burke *et al.* (2009*b*)

Par used: B, Bark; Bu, Bulb; G, Grain; L, Leaf; R, Root; EPG, Eggs per gram; FLC, Faecal Larval Counts; RAW, Reduction Adult Count; PEG, Polyethylene Glycol; DM, Dry Matter; BW, Body Weight; CT, Condensed Tannins

and changes in the anterior part of the digestive tract may interfere with parasite nutrition and consequently lead to malnutrition, reduced fertility and mortality (Martínez-Ortíz-de-Montellano *et al.*, 2013).

The second most found metabolite with anthelmintic activity in goats was the flavonoid. Flavones of the *Turnera ulmifolia* reduced egg hatch, larval development and larval motility of *H. contortus* (Oliveira *et al.*, 2017). Santos *et al.* (2017) have also suggested that flavones (tricin and diosmetin) are related to the anthelmintic activity of *Digitaria insularis*. The extracts of the waste of *Agave sisalana* showed *in vitro* activity on two different stages of the GIN of goats, and their possible active ingredients are flavonoids and saponins (Botura *et al.*, 2013). Thus, saponin is the third class of metabolites most found in plants with anthelmintic activity. Gomes *et al.* (2016) reported this activity of *Zizyphus joazeiro* on eggs of *H. contortus*.

De Medeiros *et al.* (2018) evaluated the *in vitro* effect of water-soluble *Moringa oleifera* lectin (WSMoL) on hatching of eggs and on the development of early-stage larvae of gastrointestinal nematodes from naturally infected goats. The mechanism of action of this substance is attributed to the interference of WSMoL on the activity of proteases and the affinity of the lectin for glycosylated, interacting with intestinal glycoconjugate receptors in the embryo, as well as in cuticle of the larvae.

The extracts rich in sesquiterpene lactones of two forage chicory (*Cichorium intybus*) showed inhibition of hatching of a predominantly *H. contortus* egg population. The most active cultivar presented higher concentration of the 8-deoxylactucin. This action is associated to the presence of α-methylene-γ-lactone functional group capable of reacting with sulfhydryl proteins (Foster *et al.*, 2011).

Two studies have demonstrated the anthelmintic activity of essential oils in goats, obtained from the species *Eucalyptus staigeriana* (Macedo *et al.*, 2010) and *Juniperus pinchotii* (Armstrong *et al.*, 2013). The antiparasitic effect of these plants has been related to the presence of terpenoids (lemonene, eugenol, carvacrol and citral). The chemical substances of this class can act by inhibiting the growth, reducing the reproductive capacity or causing damage during parasite maturation process (Zhu *et al.*, 2013).

Only two studies that used isolated substances of plants were found in this review. Santos *et al.* (2018) used two isolated saponins and presented effect above 90% for egg hatch inhibition (aescin) and larval motility inhibition (digitonin). These authors attributed the anthelmintic effect of saponin to their ability to form complexes with cellular membrane components leading to a pore formation and consequent increase in membrane permeability. The second work was performed by Soldera-Silva *et al.* (2018), who tested quercetin, rutin and epicatechin against *H. contortus* larval. They observed high efficacy with low EC_{50} of 7.8, 30 and 10 μg mL^{-1}, respectively.

The therapeutic properties of plants can be attributed to one substance or combination of compounds produced by the secondary metabolism of the plant. Klongsiriwet *et al.* (2015) reported the synergistic effects between the fraction of condensed tannins and two flavonoids, quercetin and luteolin, in terms of inhibiting the *in vitro* exsheathment of *H. concortus* L_3 larvae obtained from small ruminants. The complexity and diversity of structures of the phytocompounds could enable their interaction with multiple molecular targets on the parasite and may consequently hinder the appearance of populations resistant to these substances (Chan-Pérez *et al.*, 2016).

The *in vitro* studies are indicated as screening tests, which must be performed prior to the *in vivo* evaluation. The *in vitro* tests cannot be enough to confirm anthelmintic efficacy of plants, since *in vitro* conditions are different from *in vivo* experiments,

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particularly due to the gastrointestinal tract of ruminants. Therefore, pharmacokinetic studies should be carried out for the determination of the natural product bioavailability in small ruminants (Githiori *et al*., 2006).

In vivo *studies of the anthelmintic activity of plants in goats*

The *in vivo* evaluation of the activity of plant against the GIN of goats has been performed mainly by means of FECRT and controlled tests (Githiori *et al*., 2006). The results obtained in the FECRT cannot estimate anthelmintic efficacy accurately because egg count does not always correlate well with worm numbers. The controlled test is considered as more reliable because the efficacy was measured by the count of adult parasite in the gastrointestinal tract and the evaluation of egg output (Taylor *et al*., 2002).

The species *Quercus leucotricophora, Q. semecarpifolia* and *Desmodium intortum* induced a reduction of EPG, whereas *Bauhinia pulchella* promoted a reduction of egg viability and pasture contamination (Debela *et al*., 2012; Raju *et al*., 2015; Lopes *et al*., 2016). Other plants, such as *A. karroo* and *Lespedeza cuneata,* demonstrated effect against adult parasites (Marume *et al*., 2012; Gujja *et al*., 2013). In this review, we observed that some plants, as *A. sisalana, A. mearnsii, A. nilotilica*, were able to promote reduction in the egg count, but did not interfere in the worm burden. The reduction of EPG can be related to a reduction in the nematode burden or a lower fecundity of female worms (Githiori *et al*., 2006).

There is a lack of specific guidelines for assessing the anthelmintic effect of plant-derived products. The present work identified variations in the protocols applied for *in vivo* studies, especially treatment time, dosage, number of animals, plant preparation and parameters evaluated.

Most of the plants evaluated *in vivo* contain tannin in their chemical composition, and the treatment consisted of the administration of the plant in animal feed. The treatment of goats with leaves of *Bauhinia pulchella* (180 mg kg^{-1} per 63 days), rich in condensed tannins, showed reduction in egg viability and pasture contamination of *T. colubriformis* (86%) (Lopes *et al*., 2016). The administration of the commercial extract of *A. mearnsii* (24 g $animal^{-1}$ day^{-1}), containing 16.7% of tannins, for an extended period (27 weeks) resulted in the reduction of EPG in the first half of the experimental period. However, there was no effect on the parasite count of adults recovered from goats (Costa-Júnior *et al*., 2014). The supplementation of goats with sorghum grains, containing high levels of condensed tannins, and the administration of commercial preparation of condensed tannins obtained from the bark of *A. mearnsii* did not significantly influence EPG (Whitley *et al*., 2009; Max, 2010). According to Costa-Júnior *et al*. (2014), the continuous consumption of tannin may cause an increase in the concentration of salivary proteins, especially in growing animals. These proteins have high affinity for tannin, which can lead to reducing the effect of this active compound.

The addition of *Lespedeza cuneata* hay in the goat diet, in the concentration of 50 to 75%, caused reduction of EPG 84.6 and 91.9%, respectively. Only the treatment with the highest concentration resulted in a significant decrease of the number of adult parasites (74%) (Terrill *et al*., 2009). In goats, fed pellets with the same species, a significant reduction in the EPG (58 to 70.9%), though there was no reduction in the number of *H. contortus* in the abomasum. The analysis of parasites by electron microscopy revealed changes in the cuticle (constricted folds and a disheveled cuticular surface appearance) (Kommuru *et al*., 2014, 2015).

Most of the species compiled in this study belong to the family Fabaceae, which presents worldwide distribution. This family includes herbaceous plants, trees and shrubs (perennials or annuals). Some species are used as feed for small ruminants. These plants have agronomic characteristics that could provide beneficial effects to the nutrition and health of animals and environmental issues: palatability for ruminants and nutritive values; biological nitrogen fixation, which reduces the use of chemical fertilizers; carbon sequestration; provision of shade for livestock and flowers for pollinators; conservation of the biodiversity, reduction of methane emission and greenhouse gases (Fagbenro *et al*., 2015; Hoste *et al*., 2015). The legume species, *Lespedeza cuneata*, has been widely studied and has shown some advantages as the ability to produce seeds and to be cultivated efficiently, as well as the viability of large-scale production (Hoste *et al*., 2015). Puchala *et al*. (2005) observed lower methane emissions from goats fed on lespedeza (*Lespedeza cuneata*) and this effect was related to the presence of condensed tannins in the plant.

The use of forage legumes rich in condensed tannins as nutraceutical plants (species that present positive effects for animal nutrition and health) has been proposed to control GIN in small ruminants. Hoste *et al*. (2006) suggested that feeding small ruminants with tannin-rich plants (30–40 g of condensed tannins per kg dry matter) promotes antiparasitic effect. However, the excessive consumption of tannin can cause antinutritional effect in animals. The condensed tannins, at higher concentrations (7–8% DM), can depress feed intake, disturb digestive physiology and decrease nutrient digestibility and the production rate (Min *et al*., 2003).

Other classes of substances have been associated with anthelmintic activity in goats, such as saponin and essential oils. The treatment of goats naturally infected with gastrointestinal nematodes, with the aqueous extract obtained from the residue *Agave sisalana* (1.7 g kg^{-1} per 8 days), led to a reduction of EPG (50.3%) but did not affect the number of adult parasites. This anthelmintic effect was associated with the presence of saponins in this extract (Botura *et al*., 2011). The oral administration of essential oil obtained from the leaves *E. staigeriana* (500 mg kg^{-1}) resulted in a significant reduction of EPG (76.5%) in goats. The chemical constituents present in the oil associated with this activity were the citral and limonene (Macedo *et al*., 2010).

Differences in anthelmintic efficacy of several plants were verified between the *in vitro* and *in vivo* studies, such as *A. sisalana, A. nilotica, C. vulgaris* and *L. latisiliquum,* which were more active in *in vitro* assays. The treatment *in vitro* is characterized by direct contact with the parasites and the concentrations of potentially active substances do not always correspond to their *in vivo* bioavailability (Githiori *et al*., 2006). Furthermore, the possibility of biotransformation of these compounds within the gastrointestinal tract of the animal, modified by rumen microorganism, may lead to a reduction of biological activity (Athanasiadou and Kyriazakis, 2004).

Most studies on potential *in vivo* anti-parasitic plants have showed lower percentage of efficacy to synthetic drugs. An anthelmintic product is considered as effective when it has a percentage reduction of over 90% of EPG and adult parasites (Vercruysse *et al*., 2001). The treatments with *Vigueira dentata*, *Lespedeza cuneate, Elephantorrhiza elephantina, Gymnopodium floribundum* and association of *Leucaena leucocephala* and *Mimosa bahamensis* exhibited reduction of EPG over 90%, whereas only one species, *A. karroo*, induced 90% of reduction of adult nematodes (Marume *et al*., 2012; Maphosa and Masika, 2012b; Gujja *et al*., 2013; Ventura-Cordero *et al*., 2017). Githiori *et al*. (2006) suggest that a lower level of reduction should be established (70%) to the evaluation tests *in vivo* herbal preparations, since products with moderate anthelmintic activity may be part of an integrated

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program of parasite control in ruminant production systems. The integrated management is the combination of chemical and non-chemical methods of parasite control in order to maintain acceptable levels of production without total elimination of the parasites (Hoste and Torres-Acosta, 2011).

The sustainable control of GIN infection must be guided by three principles: management of grazing systems; stimulation of host response and modulation of worm biology (Hoste *et al.*, 2015). The reduction of contact with infective larvae (L_3) can be achieved by strategies of grazing management such as pasture rotation system and mixed grazing. As the L_3 survives on pastures for a limited period of time, the pasture rotation can cut down on the number of parasites ingested by the animal. It has better applicability in tropical climate. Mixed grazing among different animal species or by older animals may also be an alternative for the reduction of L_3 because GIN presents a relative specificity for its hosts. However, mixed grazing between sheep and goats should be avoided due to the strong overlapping of nematodes infecting these two hosts (Torres-Acosta and Hoste, 2008; Hoste and Torres-Acosta, 2011). Another measure for parasite control is the use of organisms that aim at altering the biology of the free-living stages in the environment, decreasing the pasture infectivity. Amongst the various potential agents, one of the most extensively studied models is the use of nematophagous fungi, as *Duddingtonia flagrans*, which has the ability to invade and kill nematode larvae in the faeces (Sanyal *et al.*, 2008).

The stimulation of immune response has been proposed to aid in the control of GIN infection in small ruminants, particularly the genetic selection of resistant animals and the manipulation of host nutrition. This strategy is important for goats since their immune response against GIN is less effective than that observed in sheep. Variability in host response is associated with several factors, such as herbivore behaviors (grazing and/or browsing), age, previous contact with parasites, gender, breed or individual genetic characteristics, nutrition status and the presence of other parasites (Torres-Acosta and Hoste, 2008).

Conclusions/Future directions

Almost all the plants described in this review showed promising anthelmintic effects, especially *in vitro* studies. However, *in vivo* trials, generally, report lower plant efficacy, probably due to the interference of pharmacokinetic parameters of ruminants in the bioavailability of active compounds of plants. This work also noticed that there is a lack of studies on the effect of chemical constituents isolated from plants against GIN. Condensed tannins were the metabolite class most related with anthelmintic activity, followed by saponins and flavonoids. Studies on the mechanisms of action are required to improve our understanding of interactions between plant secondary metabolites and the different parasitic stages and species. Moreover, efforts should be performed to standardize the formulations of products derived from plants and the validation of their use as anthelmintic in goats. Plants are an important source of new bioactive molecules and may be useful as a part of integrated parasite control, which would lead to the reduction of the use of synthetic anthelmintic drugs.

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