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Efficacy, toxicity, and lethality of plants with potential anthelmintic activity in small ruminants in Brazil

Eficácia, toxicidade e letalidade de plantas com potencial atividade anti-helmíntica em pequenos ruminantes no Brasil

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SUMMARY

The use of medicinal plants as a therapeutic method in the control of diseases has been increasing in animal production. In the case of small ruminants, the endoparasitic disease is a major concern, since they are considered the greater sanitary problem, especially when considering the phenomenon of parasite resistance to the medicines used. Therefore, the development of alternative methods of endoparasitary control in goats and sheep has become a pressing need. The use of plants to control endoparasites can reduce the use of chemical inputs, making more environmentally sustainable livestock, minimizing the occurrence of parasitic resistance to conventional medicines and contributing to the reduction of production costs. In this sense, several studies have been carried out in order to evaluate the *in vitro* and *in vivo* activity of plants with anthelmintic potential. However, despite the potentiality found in many studies, the results are sometimes contradictory or do not replicate *in vivo* the same efficacy obtained in the *in vitro* assays. Another relevant aspect is the low utilization of the lethality and toxicity tests, which are indispensable so that the knowledge can be spread and applied by the producers in their herds. Thus, this review aims to provide the results from studies carried out in Brazil with extract of plants with potential for control of parasitic disease in goats and sheep, describing the main evaluated plants species, mechanisms of action, preparation forms and tests of efficacy, toxicity, and lethality.
Keywords: antiparasitics, biological assays, goat, medicinal plants, sheep

RESUMO

A utilização de plantas medicinais como método terapêutico no controle de enfermidades tem sido crescente na produção animal. No caso de pequenos ruminantes, as verminoses representam uma grande preocupação, visto que são consideradas o maior problema sanitário, especialmente quando se considera o fenômeno da resistência dos parasitas aos fármacos utilizados. Portanto, o desenvolvimento de métodos alternativos de controle endoparasitário em caprinos e ovinos tem se tornado uma necessidade premente. O uso de plantas para controlar as endoparasitoses pode reduzir o uso de insumos químicos, tornando a atividade pecuária mais ambientalmente sustentável, minimizando a ocorrência da resistência parasitária aos medicamentos convencionais e contribuindo para redução dos custos de produção. Nesse sentido,

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diversos estudos têm sido executados a fim de se avaliar a atividade *in vitro* e *in vivo* de plantas com potencial anti-helmíntico. Contudo, a despeito da potencialidade verificada em muitos estudos, os resultados são, por vezes, contraditórios ou não reproduzem *in vivo* a mesma eficácia obtida nos ensaios *in vitro*. Outro aspecto relevante é a baixa utilização dos testes de letalidade e toxicidade, indispensáveis para que o conhecimento possa ser difundido e aplicado pelos produtores rurais. Assim, essa revisão visa fornecer os resultados obtidos nos estudos realizados no Brasil com extratos de plantas com potencial para controle de verminose em caprinos e ovinos, descrevendo as principais espécies vegetais avaliadas, mecanismos de ação, formas de preparo e os testes de eficácia, toxicidade e letalidade.

Palavras-chave: antiparasitários, ensaios biológicos, caprinos, plantas medicinais, ovinos

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INTRODUCTION

Small ruminant husbandry in Brazil has increased and contributes to the maintenance of small family-managed rural properties. The most recent agricultural census conducted in 2017 counted 8,252,706 goats and 13,770,344 sheep distributed in all states, with the largest herd recorded in the northeast region (SIDRA-IBGE, 2018).
The production and consumption of goat-sheep products should expand because of not only the natural growth of the population but also the organizational trend in the sector, which has great economic potential (Souza et al., 2016). However, challenges such as diseases can limit or economically harm sheep and goat husbandry (Sprenger et al., 2015).
Parasitism is a major factor limiting livestock production in general. The goat and sheep industry are affected by many parasites representing significant losses in meat, milk and wool culture (Ataide and Cansi, 2013). Notwithstanding the availability of alternative methods to control and treat parasitic diseases (Molento et al., 2011), allopathic drugs remain the main choice for this purpose (Melo et al., 2015; Costa et al., 2017).
World trade in animal health drugs reached US $30 billion in 2016 (Statista, 2018), with an upward projection of expenditures estimated at US $54 billion/year by 2027 (FMI, 2017). In Brazil, the industry net billing in this sector in 2017 was approximately US $1,4 billion, of which 27,2% was related to trade in antiparasitic products (SINDAN, 2018).
The indiscriminate use of antiparasitic drugs is associated with the high resistance currently observed in parasites, which can cause great economic losses as it reduces animal productivity and increases costs following non-effective treatments (Molento et al., 2013).
Studies of plants with antiparasitic medicinal potential have been seeking to reduce treatment costs and environmental contamination (Eguale et al., 2007). Assays using plant extracts have shown satisfactory results in reducing endoparasitism (Rodrigues et al., 2007; Peneluc et al., 2009, Silva et al., 2010). Phytochemical studies, which involve isolation of plant extract constituents with anthelmintic potential (Cordeiro et al., 2010), are a valuable initial step in determining the *in vitro* efficacy and toxicity followed by *in vivo* evaluations (Andrade et al., 2014). This review aims to provide the results from studies carried out in Brazil with extract of plants with potential for control of parasitic disease in goats and sheep, describing the main evaluated plants, mechanisms of action, preparation forms and tests of efficacy, toxicity, and lethality.

METHODOLOGY

For the accomplishment of this review, scientific articles related to plants with anthelmintic potential in goats and sheep were searched in six scientific portals: Google Academic, Capes Periodicals, Lilacs, Scielo, Pubmed and Science Direct journals. The following keywords were used: extracts, plants, antihelmintics, anti-parasites, goats, sheep, Brazil. Publications were searched in Portuguese, English, and Spanish from 2000 to 2018. Articles with biological assays (*in vivo* and / or *in vitro)* were considered; duplication articles, undergraduate studies, theses, dissertations, reviews, and works presented in events were used as exclusion criteria. From these criteria,

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48 articles were selected to form the basis of this review.

MAIN PLANTS EVALUATED FOR ANTHELMINTIC EFFECT IN SMALL RUMINANTS AND MECHANISM OF ACTION OF THEIR ACTIVE FRACTIONS

Many plant species have been studied to verify their anthelmintic effects in Brazil. Among the 50 plants listed in this study (Figure 1), *Operculina halmiltonii* is the most widely studied species (8.6%), followed by *Mormodica charantia*, *Musa* sp., *Azadirachta indica*, *Agave sisalana*, and *Allium sativum*. These plants are also found in other countries (Zhang et al., 1996, Hammel, 2010, Davidse et al., 2012, Karuppiah and Mustaffa, 2013, Wang et al., 2014), and many of them have been the subject of research in this field (Fang et al., 2007, Karuppiah and Mustaffa, 2013, Wang et al., 2014).

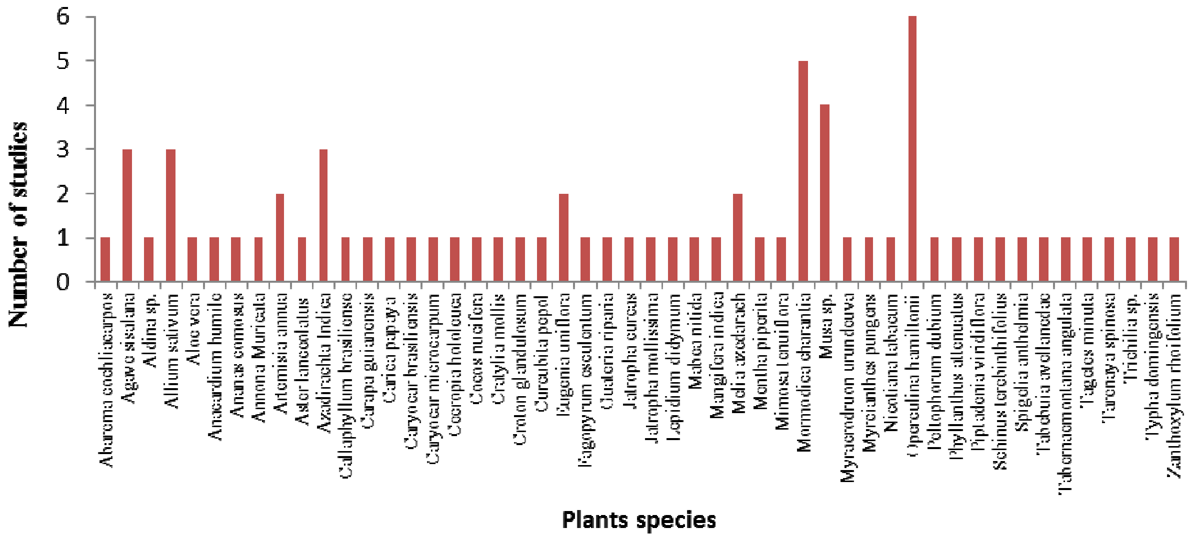

Figure 1. Number of studies of plants with anthelmintic activity in goats and sheep carried out in Brazil, from 2000 to 2018

Operculina halmiltonii, commonly found in the North and Northeast regions of Brazil (Braga, 1960), has shown mixed results in antiparasitic efficacy tests (Almeida et al., 2007; Rodrigues et al., 2007; Gomes et al., 2010; Silva et al., 2010; Araújo et al., 2011; Brito-Júnior et al., 2011). The anthelmintic activity of this plant is attributed to the presence of condensed tannins in its composition (Silva et al., 2010, Nogueira et al., 2012), which may act by expelling parasites or reducing female fecundity (Shalders et al., 2014).

Condensed tannins promote adherence between the extract and larvae, preventing its motility and feeding, resulting in energetic stress and death of the parasite (Gomes et al., 2010). The interaction with the proteins of the cuticle, oral cavity, esophagus, cloaca, and vulva of the nematodes are described as tannins direct actions. While reducing the amount of digested protein in the rumen and increasing its availability in the small intestine, favoring the host's antiparasitic immune response, are described as indirect

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actions of these metabolites (Hoste et al., 2006). The use of a tannin inhibitor, such as polyvinylpyrrolidone, together with plant extracts with known anthelmintic action, was able to reduce the activity of the product, thus demonstrating the real anthelmintic effect attributed to the tannins (Oliveira et al., 2011).

The antihelminthic effect of *Mormodica charantia* has been evaluated previously in caprine species (Almeida et al., 2007; Cordeiro et al., 2010; Gomes et al., 2010; Brito-Júnior et al., 2011) and showed contrasting results. These differences may be due to the plants used in the studies presenting active ingredient in different concentrations since they came from regions with different edaphoclimatic conditions (Furtado et al., 2013). The triterpene glycosides and mormodicins I and II are main secondary metabolites responsible for nematicidal action (Beloin et al., 2005), although tannins are abundant in this plant extract (Gomes et al., 2010). The interaction of several chemical groups on different compounds may enable activity toward multiple molecular targets at different stages of parasite development (Marie-Magdeleine et al., 2009).

Musa sp. has been the subject of several studies showing contrasting results (Oliveira et al., 2010; Parra et al., 2011; Silva et al., 2013; Gregory et al., 2015). These differences may be because different parts of the plant were used and/or the soil and climate conditions differed during the sampling period (Furtado et al., 2013). Phytochemical analyses showed that the banana pseudoculm contains polyphenolic compounds, including tannins (Lans et al., 2000), which were previously described as anthelmintic agents (Gomes et al., 2010; Shalders et al., 2014).

Azadirachta indica, which is native to the arid regions of India (Saxena, 1983), is another plant that has presented contradictory results regarding its anthelmintic action (Igarashi et al., 2013; Salas et al.; 2013, Soares Filho et al., 2015). This is likely attributed to the different concentrations of azadirachtin in the analyzed extracts. Azadirachtin, responsible for the anthelmintic effect of *A. indica*, is highly sensitive to ultraviolet radiation and acidic and alkaline media, which allow its rapid biodegradation (Neves et al., 2003). Different parts of the plants can also be a source of variation, since its present varying levels of fatty acids and metabolites associated with a nematicidal action (Salas et al., 2013). The substances contained in *A. indica* affect parasite feeding, growth, longevity, and fertility - interfering with copulation behavior, oviposition, and egg viability (El-Shafie and Basedow, 2003; Hasan and Ansari, 2011).

The antihelminthic effect of *Agave sisalana* was studied in goats (Domingues et al., 2010; Botura et al., 2011; Silveira et al., 2012) and sheep (Silveira et al., 2012) but these studies showed discordant results. *Agave sisalana* contains saponins as secondary metabolites (Francis et al., 2002). Saponins exhibit surfactant activity and form a stable foam when shaken with water, a phenomenon that can affect eukaryotic organisms, which contain steroids in their membranes (Osbourn, 1996). *Agave sisalana* is very socioeconomically important for fiber-producing municipalities in the Brazilian semi-arid region (Santos, 2006).

Allium sativum is a plant contains allicin which has anthelmintic effects. However, allicin is very unstable (Santos et al., 2011); this may explain the contradictory results obtained in previous studies (Almeida et al., 2004; Santos et al., 2011, Holsbach et al., 2013). Allicin acts on the integument of the parasite causing edema and ulcerations, which, consequently, promote greater exposure of the antigens, rendering it more vulnerable to the host's immune system (Lima et al., 2011).

Melia azedarach showed satisfactory endoparasite control results when extracts (ethanolic) were prepared from seeds and leaves (Maciel et al., 2006), in contrast to extracts prepared with the fruit *in natura* (Falbo et al., 2008). The phytochemical profile of the leaves and seeds indicated the presence of condensed tannins, triterpenoids, steroids, and alkaloids, which are associated with anthelmintic actions. Notably, the seed extract had a greater effect on egg hatchability, whereas the leaf extract was more effective in inhibiting larval development, suggesting that the leaves and seeds contain compounds with different chemical structures (Maciel et al. al., 2006).

Artemisia annua has shown contradictory efficacy in recent research using leaf extract in sheep (Cala et al., 2014; Sprenger et al., 2016). Studies to identify the metabolites responsible for the anthelmintic action revealed the presence of alkaloids, catechins, steroids, phenols, resins, tannins, and triterpenes (Sprenger et al., 2016).

PREPARATION FORMS OF PLANTS FOR USE AS ANTHELMINTICS

To evaluate anthelmintic effects, the plants have been prepared using different methods, with most (77%) studies using plant extracts. Most studies using alcoholic and hydroalcoholic extracts were conducted *in vitro*, while studies using aqueous extracts were performed *in vitro* and *in vivo* assays. When using the plants *in natura*, all studies were performed *in vivo* (Table 1).

The extraction process, which enables concentration of active principles (Coêlho et al., 2017), is divided into two stages: i) removal of the secondary metabolites from the plant using solvents and ii) evaporation of the extraction components (Santos, 2013). Although the extractive preparation methodology is relatively standardized, the substances used in the extraction process directly influences the extract yield and content of the final product (Xynos et al., 2012; Oliveira et al., 2016).

Table 1. Methods of preparation, number of studies, and evaluation types of plants with anthelmintic potential in goats and sheep, from 2000 to 2018

Preparation methods	Number of studies	Evaluation type		
		In vitro evaluation (%)	*In vivo* evaluation (%)	Joint evaluation (%)
Aqueous extracts	20	42,5	37,25	20,25
Alcoholic extracts *	13	69.24	15.38	15.38
Hydroalcoholic extracts	8	75.0	12.5	12.5
Other extracts	10	70.0	10.0	20.0
Fresh	5	0	100	0
Oil	5	66.66	33.34	0
Other preparations	5	20.0	80.0	0

* Prepared with ethanol, except for one, in which methanol was used as extractive agent.

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Egg hatchability and/or larval development was reduced by more than 80% in 88,88% aqueous extracts under *in vitro* conditions for at least one of the concentrations used (Nery et al., 2010; Oliveira et al., 2010; Ferreira et al., 2013; Salas et al., 2013; Cunha et al., 2014; Morais Costa et al., 2016). No aqueous extracts showed an RFEC (reduction faecal egg count) greater than 80% under *in vivo* conditions; however, 71.42% of the extracts had RFEC of 50–80% (Rodrigues et al., 2007; Botura et al., 2011; Domingues et al., 2013; Pereira et al., 2013; Silva et al., 2013; Mendonça-Lima et al., 2016; Coêlho et al., 2017). Only 25% of the aqueous extracts evaluated simultaneously *in vitro* and *in vivo* showed satisfactory results in both condition, with a reduction of up to 95% and 92%, respectively (Peneluc et al., 2009). Other studies reported a 90% to 100% reduction of infecting larvae *in vitro*; however, the RFEC was 53% (Nery et al., 2012), 47.20% (Morais Costa et al., 2016), and 33% (Nogueira et al., 2012).

All alcoholic extracts evaluated *in vitro* showed promising effects (Assis et al., 2003; Almeida et al., 2004; Cordeiro et al., 2010; Gomes et al., 2010; Nery et al., 2010; Araújo et al., 2011; Sprenger, 2015; Tenório et al., 2015a; Morais Costa et al., 2016). Under *in vivo* condition, just alcoholic extract of *O. hamiltonii* showed satisfactory results (Brito-Júnior et al., 2011). The alcoholic extracts used in double trials, despite having shown an *in vitro* effect, were not effective *in vivo* (Cala et al., 2014; Ribeiro et al., 2014).

Only the hydroalcoholic extracts of *Eugenia uniflora* (Hassum et al., 2013; Gonçalves et al., 2016; Sprenger et al., 2016) and *Artemisia annua* (Sprenger et al., 2016) used *in vitro* assays showed promising results. Under *in vivo* condition, hydroalcoholic extracts of *Mormodica charantia* and *Lepidium didymum* showed significant RFEC (Coêlho et al., 2017), while hydroalcoholic extract of *Tarenaya spinosa* showed phytotherapeutic potential for controlling gastrointestinal nematodes *in vitro* and *in vivo* assays (Andrade et al., 2014).

Other substances such as ethyl acetate (Assis et al., 2003; Oliveira et al., 2009), hexane (Assis et al., 2003; Maciel et al., 2006; Krychak-Furtado et al., 2011), chloroform (Assis et al., 2003; Maciel et al., 2006), acetone (Oliveira et al., 2011), dimethyl sulfoxide (Cunha et al., 2014), and dichloromethane (Cala et al., 2014) have been used as extractive agents.

Other forms of plant preparation used to evaluate the anthelmintic effect in small ruminants were: i) dehydrated leaves (Parra et al., 2011; Gregory et al., 2015) and ground (Falbo et al., 2008) and ii) dehydrated and ground fruit (Falbo et al., 2008) and juices (Almeida et al., 2004; Domingues et al., 2010; Santos et al., 2011). Using *in natura* plants, only *Curcubita pepol* showed an RFEC above 80% (Almeida et al., 2007). Oils extracted from two plants, *Carapa guianensis* (Farias et al., 2010) and *Aster lanceolatus* (Krychak-Furtado et al., 2011) showed anthelmintic effect.

Thus, although the extraction process is considerably more laborious, it is advantageous compared to the use of *in natura* plants. The extraction process may facilitate release of chemical components or active principles not released when the *in natura* plant is subjected to the digestion process (Coêlho et al., 2017).

EVALUATION OF THE EFFECTS OF TOXICITY AND LETHALITY OF PLANTS WITH POTENTIAL ANTHELMINTIC EFFECT

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Toxicity and lethality tests are designed to measure the relative toxicity of substances and prevent undesirable effects in biological systems when the plants are used therapeutically (Forbes and Forbes, 1994; Silva et al., 2016). Despite the importance of this procedure, only 18% and 8% of the studies described in this review evaluated toxicity and lethality effects, respectively.

Toxicity is defined as an inherent property of the substance which exerts harmful effects on exposed organisms during a period at a defined concentration (Dux and Stalzer, 1988). Toxicity tests in animals can evaluate the general disposition, motor coordination, muscle tone, reflexes, and activity of the autonomic nervous system (Cunha et al., 2013), as well as hematological and biochemical alterations (Soares Filho et al., 2015). Likewise, there are trials that determine the reproductive toxicity of substances on mating rates, gestation, birth rate, offspring viability, weaning rate and embryo losses (Hollenbach et al., 2015); a specific test (Hershberger's test) can identify substances with androgenic and antiandrogenic activity (SEP, 2011). In *post-mortem* examinations, these tests are still able to verify macroscopic (Hayes and Dipasquale, 2001) and microscopic alterations in affected systems and organs (Tokarnia et al., 2012).

Two plants, among those described in this review, were subjected to toxicological testing in mice. *Piptadenia viridiflora* administered for 4 days at a dose of 203 mg/kg caused no behavioral nor organic changes (Morais-Costa et al., 2016). The extract of *Cocos nucifera* did not show toxicity following oral administration (Oliveira et al., 2009).

The toxic effects of seven plants were evaluated concurrently with the anthelmintic efficacy assays in the same animals. With *Agave sisalana*, the animals were evaluated for hepatic, renal, and physiological parameters and showed normal results except for hematocrit and hemoglobin, which showed values below normal (Domingues et al., 2010; Botura et al., 2011). *Jatropha curcas*, *Tabebuia avellanedae*, and *Schinus terebinthifolius* did not change the heart rate, respiratory rate, rectal temperature, and most hematological parameters. Only *J. curcas* reduced hematocrit and total protein levels (Wolupeck et al., 2012). *Azadirachta indica* did not show alterations in globular volume, total plasma protein, total leukocytes, segmented neutrophils, lymphocytes and eosinophils, creatinine, or aspartate aminotransferase (Soares Filho et al., 2015). *Zanthoxylum rhoifolium* did not change the clinical and biochemical parameters nor reveal changes suggestive of histopathological toxicity (Peneluc et al., 2009). There was also no toxic reaction in animals treated with bromelain extracted from *Ananas comosus* (Domingues et al., 2013).

The advances and contributions obtained by using animals in experiments are widely known. However, bioethical guidelines must be followed to limit the suffering of experimental animals (Lolas, 2008; Franco et al., 2014). Many animal evaluations can be performed using other test systems that provide similar efficiency (Fiskesjö, 1985).

The toxicity of a plant can be evaluated *in vitro* with relative ease by using *Allium cepa*. In this test, the effect of the toxic substance is observed by macroscopic alterations such as color, shape, size and root deformity, as well as microscopic changes such as chromosomal aberrations and mitotic index (Longhin, 2008; Arrares and Longhin, 2012). Assays with *A. cepa* are easy, fast, and reliable, (Arrares and Longhin, 2012), and highly correlated with other test systems, including mammalian animals (Fiskesjö, 1985). Notably, no plants described in this review were subjected to the *A. cepa* assay.

Lethality is an effect that can be evaluated in animal tests to classify and catalog substances according to their lethal potential (Valadares, 2006). The signs that precede death, lethality index, mechanisms of action of the principles (Hayes and Dipasquale, 2001), and lesions observed in post-mortem histological examinations are parameters that can be observed in the lethality test (Tokarnia et al., 2012).

Only one plant described in this review was evaluated for lethality. In this study, *Cocos nucifera* extract was administered intraperitoneally to mice, and an LD_{50} of 1,233.9 mg/kg was determined (Oliveira et al., 2009). None study reported this assay on the target species of this review.

The lethality caused by a plant can be efficiently, quickly, and inexpensively tested in microcrustaceans of the species *Artemia salina* (Meyer, 1982; Pimenta et al., 2003). This method is safe and presents high specificity to detect bioactive compounds using small amounts of plant extracts (Lhullier et al., 2006; Koutsaftis and Aoyama, 2007). Although there are no studies demonstrating a direct relationship of *Artemia salina* test and a particular animal species, this bioassay has been considered to be effective in tracing substances toxic to zoological systems (Meyer, 1982).

Only four of the plants described in this review were evaluated for lethality using the *A. salina* test (Andrade et al., 2014; Ribeiro et al., 2014; Sprenger, 2015; Sprenger et al., 2016). Two plants, *T. spinosa* (Andrade et al., 2014) and *Jatropha mollisima* (Ribeiro et al., 2014), were identified as toxic, while *Aloe vera* (Sprenger, 2015) and *Artemisia annua* (Sprenger et al., 2016) showed good safety margins for animal use with a DL_{50} of >1,000 g/mL (Meyer et al., 1982). This test has not been widely used despite the ease of implementation, possibility of partitioning the bioactive principles of the plants, and ability to avoid the direct use of animals (Meyer et al., 1982).

EVALUATION OF THE *IN VITRO* EFFECT OF PLANTS

A total of 44% of the studies discussed in this review were performed exclusively *in vitro* to evaluate the reduction of viable egg counts by hatchability, larval development (from L1 to L3 larval stage), and motility of adult worm tests (Table 2).

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Table 2. List of plants with anthelmintic potential in goats and sheep tested exclusively *in vitro* and maximum activity obtained in the studies, from 2000 to 2018

Plant	Part of plant used	Tests used	Maximum activity (%)	Author
Aster lanceolatus	Flowers	Hatchability	91	Krychak-Furtado et al., 2011
Operculina halmiltonii	Tubercle	Hatchability	70.4	Araújo et al., 2011
			78.69	Gomes et al., 2010
		Larval development	66.8	Araújo et al., 2011
			33.34	Gomes et al., 2010
Mormodica charantia	Leaves	Hatchability	35.47	Gomes et al., 2010
			44.9	Cordeiro et al., 2010
		Larval development	80.02	Gomes et al., 2010
			86.71	Cordeiro et al., 2010
Azadirachta indica	Seeds	Hatchability	80	Salas et al., 2013
		Larval development	100	
Melia azedarach	Leaves	Hatchability	100	Salas et al., 2013
		Larval development	91.64	
	Seeds	Hatchability	100	
		Larval development	93.48	
Artemisia annua	Leaves	Hatchability	93.22	Sprenger et al., 2016
		Larval development	90.33	
Myracrodruon urundeuva	Leaves and stem	Hatchability	97.73	Oliveira et al., 2011
		Larval development	83.56	
Nicotiana tabacum	Leaves	Hatchability	99	Salas et al., 2013
		Larval development	LT50 = 8±1 min.*	
Aloe vera	Pulp	Hatchability	94.35	Sprenger, 2015
		Larval development	76.03	
Annona muricata	Leaves	Hatchability	84.91	Ferreira et al., 2013
		Larval development	89.08	
Spigelia anthelmia	Aerial Part	Hatchability	100	Assis et al., 2003
		Larval development	84.4	
Fagopyrum esculentum	Seeds	Hatchability	19.66	Gonçalves et al., 2016
		Larval development	17.66	
Agave sisalana	Leaves	Hatchability	100	Silveira et al., 2012
		Larval development	100	
Carapa guianensis	Seeds	Hatchability	100	Farias et l., 2010
		Larval development	98.3	
Musa sp.	Residues	Larval development	96	Oliveira et al., 2010
	Fruit		20.44	Silva et al., 2013
Allium sativum	Garlic	Larval development	99.34	Almeida et al., 2004
Anacardium humile	Leaves	Larval development	99.6	Nery et al., 2010
Cecropia hololeuca	Leaves	Larval development	8.10	Silva et al., 2013
Abarema cochliacarpos	Stem	Larval development	100	Tenório et al., 2015a
Eugenia uniflora	Leaves	Larval development	14,87	Tenório et al., 2015b

*Lethal Time 50 = Time required for death of 50% of the population evaluated, in minutes, with extract concentration of 500–1000 ppm.

In vitro tests enable detection of anthelmintic properties in plant extracts, consisting of a preliminary step to characterize the possible active compounds present in plants with the potential to control parasitosis (Costa et al., 2002).

Extracts of *Aldina* sp., *Phyllanthus attenuates*, and *Mabea nitida*, *Croton glandulosum*, *Tabernaemontana angulata*, *Caryocar microcarpum*, *Callaphyllum brasiliense*, *Guatteria riparia*, and *Trichilia* sp. showed effects against *Haemonchus* sp. eggs at 100 μg/mL. However, these extracts did not inhibit larval development, even at a concentration of 200 μg/mL (Cunha et al., 2014).

Eugenia uniflora, *Mentha piperita*, *Myrcianthes pungens*, and *Peltophorum dubium* were tested at concentrations of 200, 100, 20, and 2 mg/mL on ovine gastrointestinal nematode larvae. Only *E. uniflora*, at a concentration of 200 mg/mL, significantly reduced the number of total larvae, particularly against *Haemonchus* sp. and *Tricostrongylus* sp. (Hassum et al., 2013).

EVALUATION OF THE *IN VIVO* EFFICACY OF PLANTS

In spite of the trials *in vivo* provided more accurate information regarding the effectiveness of treatment in the host organism than *in vitro* tests, only 36% of the studies reviewed here carried out such trials (Table 3).

Allium sativum administered *in natura* (Holsbach et al., 2013) or in juice form (Santos et al., 2011) did not show action for RFEC. Leaves of *S. terebinthifolius*, *T. avellanedae* bark, and seed of *Jatropha curcas* was not effective for RFEC (Wolupeck et al., 2012). Likewise, *Mimosa tenuiflora* leaves administered for 3 days did not significantly reduce infective larvae of *Haemonchus* sp. (Oliveira et al., 2013).

Table 3. List of plants with anthelmintic potential in goats and sheep tested exclusively *in vivo* and maximum effectiveness obtained in the studies, from 2000 to 2018

Plant	Part of plant used	Maximum effectiveness (%)	Animal species used	Number of animals	Author
Operculina halmiltonii	Tubercle	80.7	Goats	240	Rodrigues et al., 2007
		90	Goats	40	Brito-Júnior et al., 2011
		72.32	Goats	40	Almeida et l., 2007
	Root	84	Goats	30	Silva et al., 2010
Mormodica charantia	Leaves	40	Goats	40	Brito-Júnior et al., 2011
		79.5	Sheep	24	Coêlho et al, 2017
		63.06	Goats	40	Almeida et al., 2007
Musa sp.	Leaves	94.04	Sheep	24	Gregory et al., 2015
		81	Sheep	26	Parra et al., 2014
Azadirachta indica	Seeds	29	Sheep	32	Soares Filho et al., 2015
		37	Sheep	24	Igarashi et al., 2013
Agave sisalana	Residues	50.3	Goats	30	Botura et al.,2011
Cratylia mollis	Leaves	61.1	Goats	36	Mendonça Lima et al., 2016
Tagetes minuta	Aerial Parts	51.5	Sheep	24	Coêlho et al., 2017
Carica papaya	Seeds	70	Sheep	45	Pereira et al., 2013
Lepidium didymum	Aerial Parts	63.7	Sheep	24	Coêlho et al., 2017
Curcubita pepol	Seeds	87.31	Goats	40	Almeida et al., 2007
Typha domingensis	Rhizome	48	Goats	30	Silva et al., 2010
Melia azedarach	Fruit	33.21	Sheep	24	Falbo et al., 2008

IN VITRO VERSUS *IN VIVO* EFFECT OF PLANTS WITH ANTHELMINTIC POTENTIAL

Only 20% of the reviewed studies performed the joint evaluation (*in vitro* and *in vivo*), establishing a parallel of the results obtained with the two methodologies. Most studies (90%) did not replicate *in vivo* the promising results found *in vitro*. It is noteworthy that 80% of the studies were carried out in sheep and only 20% in goats (Table 4).

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Table 4. Maximum effectiveness of plants with anthelmintic potential in goats and sheep evaluated *in vitro* and *in vivo* assays, from 2000 to 2018

Plant	Part of plant used	Maximum effectiveness (%) *in vitro*	Maximum effectiveness (%) *in vivo*	Animal species used	Number of animals	Author
Zanthoxylum rhoifolium	Leaves		92	Goats/ Sheep*	20	Peneluc e al., 2009
Agave sisalana	Liquid Residue	>95	40	Goats	24	Domingues et al., 2010
Tarenaya spinosa	Root	81.53	41	Sheep	20	Andrade et al., 2014
Jatropha mollisima	Stem	70.77	47.1	Sheep	20	Ribeiro et al., 2014
Cocos nucifera	Fiber	10	18.69	Sheep	18	Oiveira et al., 2009
Mangifera indica	Fruit	100	53	Sheep	24	Nery et al., 2012
Caryocar brasiliensis	Bark	98.7	33	Sheep	36	Nogueira et al., 2012
Piptadenia viridiflora	Leaves	90	47.2	Sheep	24	Morais Costa et al., 2016
Ananas comosus	Bark	90	22	Sheep	36	Domingues et al., 2013
Artemisia annua	Leaves	99	19	Sheep	24	Cala et al., 2014

**In vitro* assay: goats; *In vivo* assay: sheep

FINAL CONSIDERATIONS

The use of plants with anthelmintic potential, regardless of the preparation process, has revealed the action of active substances with varying levels of efficacy in small ruminants.

Operculina hamiltonii and *Musa* sp. are effective for the reduction of endoparasitary infestation in small ruminants, and the metabolites polyphenols, including condensed tannins, are responsible for this activity. *Mormodica charantia* also presents a high activity to reduce endoparasitoses, and triterpenos glycosides and mormodicinas are the active components. *Zanthoxylum rhoifolium* and *Curcubita pepol* have high anthelmintic activity; however, there is still no description of its active components. Other plant species, cited in this review, have antiparasitic activity; yet, this effect has been determined, so far, only in vitro assays.

Considering that the metabolomic composition of plants can vary according to the environmental conditions, different edaphoclimatic conditions, use of plants at different vegetative stages or even use of different parts of the plant may be pointed out as causes of variation of results obtained in different studies carried out with the same plant.

The difficulty of *in vivo* replication of results achieved *in vitro* may be due to intrinsic factors to the animals; laboratory tests use eggs and/or larvae isolated, without the interference of the organic matter, unlike what occurs in the animals; most *in vitro* larval trials are not done with infective larvae within the parasitic cycle of worms, which may

lead to divergences with the *in vivo* assays.
The accomplishment of preliminary tests of toxicity and lethality of the plants and their derivatives are needed to ensure the welfare of animals undergoing experimentation.
Notwithstanding some species of plants with taniferous contents present high anthelmintic activity, studies on the substances responsible for this action are lacking. The identification and isolation of these active molecules will aid in the promotion of medicinal plants and, possibly, in the investment for the production of natural anthelmintic substances.

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