frontiers
in Pharmacology

A Systematic Review on Comparative Analysis, Toxicology, and Pharmacology of Medicinal Plants Against *Haemonchus contortus*

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Background: *Haemonchus contortus* is an important pathogenic nematode parasite and major economic constraint of small ruminants in tropics and subtropics regions. This review is an attempt to systematically address the; (a) efficacy of different plants against *H. contortus* by *in vitro* and *in vivo* proof; (b) toxicology, mechanism of action, and active phyto-compounds involve in anti-haemonchiasis activity; (c) and comparative analysis of plant species evaluated both *in vitro* and *in vivo*.

Methods: Online databases (Google Scholar, PubMed, Scopus, and ScienceDirect) were searched and published research articles (1980–2020) were gathered and reviewed.

Results: A total of 187 plant species were reported belonging to 59 families and 145 genera with Asteraceae and Fabaceae being frequently used. Out of the total plant species, 171 species were found to be evaluated *in vitro* and only 40 species *in vivo*. Twenty-four species were commonly evaluated for *in vitro* and *in vivo* anti-haemonchiasis activity. Among the reported assays, egg hatching test (EHT) and fecal egg count reduction (FECR) were the most widely used assays *in vitro* and *in vivo*, respectively. Moreover, sheep were the frequently used experimental model *in vivo*. After comparative analysis, *Lachesiodendron viridiflorum*, *Corymbia citriodora*, *Calotropis procera*, and *Artemisia herba-alba* were found highly effective both *in vitro* and *in vivo*. *L. viridiflorum* inhibited enzymatic activities and metabolic processes of the parasite and was found to be safe without toxic effects. *C. citriodora* was moderately toxic *in vivo*, however, the plant extract produced promising nematicidal effects by causing muscular disorganization and changes in the mitochondrial profile. Additionally, *C. procera* and *A. herba-alba* despite of their high anti-haemonchiasis activity were found to be highly toxic at the tested concentrations. *C. procera* caused perforation and tegumental disorganization along with adult worm paralysis. Nineteen compounds were reported, among which anethole and carvone completely inhibited egg hatching *in vitro* and significantly reduced fecal egg count, decreased male length, and reproductive capacity of female *in vivo*.

Conclusion: This review summarized different medicinal plants owing to nematicidal activities against *H. contortus* eggs, larvae, and adult worms. Plants like *L. viridiflorum, C. citriodora, C. procera,* and *A. herba-alba*, while compounds anethole and carvone having promising nematicidal activities and could be an alternative source for developing novel drugs after further investigation.

INTRODUCTION

Haemonchus contortus is the causative agent of haemonchiasis usually known as "twisted barber" pole worm or stomach worm (Saminathan et al., 2015), and a common blood feeder of small ruminants. The parasite is present throughout the tropical and subtropical regions of the world where it is a major constraint for profitable production of sheep and goats (Zenebe et al., 2017). Haemonchiasis is characterized by severe anemia, leading to a serious impairment of the animal, severe economic losses, and acute disease outbreaks with high death rate particularly in young animals (Selemon, 2018). Among the parasitic diseases, gastrointestinal nematode infections remain one of the main causes of impaired production in small ruminants (Hounzangbe-Adote et al., 2005). According to the pharmaceutical companies the annual cost of antiparasitic compounds is proposed to be tens of billions of dollars worldwide (Wolstenholme et al., 2004). However, the annual treatment cost of *H. contortus* has been estimated to be 26 million USD in Kenya, 46 million USD in South Africa, and 103 million USD in India (Peter and Chandrawathani, 2005).

To overcome the major economic losses in agriculture, it is essential to enhance the control of key parasitic diseases (Gilleard, 2006). For this purpose, various approaches are being in use to control parasitism, including biological control, pasture management, dietary management, vaccination, and the use of anthelmintic chemicals. Most widely used practice being followed nowadays is the use of anthelmintic chemicals. Unfortunately, regular and indiscriminate administration has posed a variety of problems including emergence of resistance in nematode parasites, e.g. multi resistant *H. contortus* has been reported. Furthermore, the commercially available anthelmintics drugs are somewhat costly and smallholder farmers are unable to expend meager income for purchasing of drugs to carry on regular treatment (Irum et al., 2015).

As a result, there is a dire need to develop alternative anthelmintic approaches from natural flora which can be less toxic, biodegradable, environmental friendly, and to cover the most challenging problem of parasite resistance issue (Carvalho et al., 2012). Worldwide, different plant species have been reported and evaluated for natural bio-products to control the parasitic infections and reduce the dependency on conventional chemotherapy. Testing for biological activity *in vitro* and *in vivo* has to be done after a purification process in order to exclude interference with accompanying compounds and reference standards for quality control of herbal medicines largely depend on isolated compounds with documented purity (Bucar et al., 2013). The compounds from plants have also been found to be

synergistic enhancers in that though they may not possess any anthelmintic properties alone, but when used concurrently with standard drugs they enhance the activity of the drug. The synergistic effect of the association of an anthelmintic drug and plant extracts against resistant pathogens leads to new choices for the treatment of infectious diseases. Also synergy between bioactive plant product and antiparasitic will confront problems of toxicity and overdose since lesser concentrations of two agents in combination are required, due to these reasons, there is need for continuous exploration of multidrug resistance modulating principles from plants sources (Aiyegoro and Okoh, 2009). The herbal medicines however, suffer from lack of standardization parameters. The main limitation is the lack of standardization of raw materials, processing methods and the final products, dosage formulation, and the non-existence of criteria for quality control (Sachan et al., 2016).

Recently, the interest of researchers in exploring the antiparasitic properties of ethnoveterinary medicinal plants is increasing and this field of research is inundated with ethnopharmacological studies. This review is aimed to gather fragmented literature about the; (a) efficacy of different plants against *H. contortus* by *in vitro* and *in vivo* proof; (b) toxicology, mechanism of action, and active phyto-compounds involve in anti-haemonchiasis activity; (c) and comparative analysis of plant species evaluated both *in vitro* and *in vivo*. Moreover, the study also highlights existing knowledge gaps in the present research and provides future recommendations to fulfill those gaps.

METHODOLOGY

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). No protocol was followed for conducting this systematic review. The PRISMA check list is provided in the supporting information section (**Supplementary Table S1**).

Databases and Searching Criteria

To find the published literature, a systematic search was performed using different databases, including Google Scholar, PubMed, Scopus, and ScienceDirect. Research articles published in English language from 1980 to 2020 were gathered for this systematic review. Key words such as: anthelmintic activity, nematicidal activity of plants, medicinal plants used for *H. contortus*, *in vitro/in vivo* efficacy of plants against *H. contortus*, active compounds in plants, mechanism of

plant extract inhibition and toxicity of plants. "Anthelmintic AND *Hemonchus contortus*", "Natural nematicidal OR anti-haemonchiasis NOT synthetic", "Natural *in vitro* OR *in vivo* anthelmintic". Bibliographies of research articles were also searched and relevant references were extracted and downloaded. Moreover, to support the findings of the review further literature search was conducted and relevant articles were included.

Inclusion/Exclusion Criteria

Research articles describing (a) *in vitro/in vivo* efficacy of medicinal plants against *H. contortus*, (b) containing full information regarding plant name, country name, extract, concentration, inhibition, time exposure, and assay type, (c) original research articles, (d) and published in English language were included in this systematic review. While articles with (a) epidemiological and molecular dataset of *H. contortus*, (b) antiparasitic activities other than *H. contortus*, (c) synthetic drugs/chemicals tested against *H. contortus*, and (d) language other than English were excluded.

Data Extraction

Endnote (Thomson Reuters, San Francisco, CA, United States) was used to compile the articles. Researchers very carefully extracted all the data from the selected articles including author (s) name, country name, plant name, family name, plant part used, plants' life form, extract used, concentration, time exposure, inhibition, and year of publication. Data were arranged into tables and figures. Chemical structures of the compounds were drawn using MarvinSketch (18.24.0) (https://chemaxon.com/products/marvinn) and Inkscape (0.92) (https://inkscape.org/) was used to further refine and improve the resolution of each chemical structure. PubChem (https://pubchem.ncbi.nlm.nih.gov) was also used to attain the IUPAC name (s) of pure compounds reported in this review.

Taxonomic Clarification

Plant scientific names, synonyms, and families were searched and corrected using "the plant list" (http://www.theplantlist.org), "tropicos" (http://www.tropicos.org), "world flora online" (http://www.worldfloraonline.org), and "Medicinal Plant Name Services-KEW" (https://mpns.science.kew.org/mpns-portal).

Quantitative Analysis

Jaccard Similarity Index (JI)

Jaccard similarity index was calculated to determine the similarity between the two sets of studies reported in this review. One set of study is the "*in vitro* pharmacological validation of medicinal plants" and the other one is the "*in vivo* pharmacological validation of medicinal plants". JI was calculated by using the formula (Kayani et al., 2015):

$$JI = c \text{ multiply } 100/a + b - c$$

Where "a" is the total number of plant species used *in vitro*, "b" is the total number of plant species used *in vivo* as anthelmintic against *H. contortus*, and "c" is the number of plant species common to both *in vitro* and *in vivo* studies.
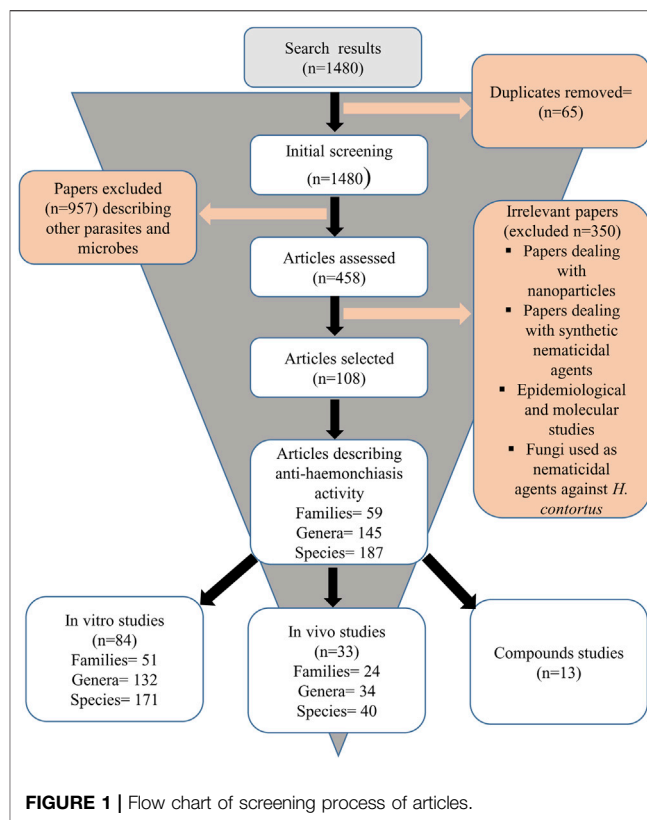

FIGURE 1 | Flow chart of screening process of articles.

RESULTS

We identified a total of 1,480 published articles through literature search. After removing duplicates, and irrelevant articles, a total of 108 articles were selected for this review (**Figure 1**). Quality assessment of the selected articles was performed and summarized as author name, species/compound(s) stated in the article, plant source, species authentication, quality control as well as chemical analysis reported (**Table 1**).

Taxonomic Clarification

According to the modern botanical nomenclature, 53 reported plant species have a synonym issue. Plant accepted names are mentioned in table (**Table 1**; **Supplementary Tables S2, S3**), while the synonym mentioned in the original articles were put into brackets. In addition, taxonomic corrections regarding the author of those plants and their family names were also revised.

Pharmacological Validation of Medicinal Plants Against *H. contortus*

Total of 187 plant species belonging to 59 families and 145 genera were tested against different life stages of *H. contortus* (**Supplementary Tables S2, S3**). Major contributed families with their species were Asteraceae (*n* = 29), Fabaceae (*n* = 19), Lamiaceae (*n* = 12), and Euphorbiaceae (*n* = 6). Different life forms of plants reported were herbs, trees, and shrubs 40, 31.4, and 27% in accordance of their order. Leaves were the most

TABLE 1 | Quality assessment of the articles selected for this systematic review.

Study	Species/compound stated in the article	Plant source	Authenticated species	Quality control reported?	Chemical analysis reported?
Cala et al. (2012)	*Melia azedaracha* L *Trichilia claussenii* C	Not stated	–	Yes	Yes-liquid-liquid chromatography
Irum et al. (2015)	*Artemisia vestita* Wall ex Besser *Seriphidium maritimum* (L.) Poljakov (=*Artemisia maritima* L.)	Collected from northern areas of Pakistan	+	No	No
Jaheed et al. (2019)	*Balanites egyptiaca* (L.) Delile	Purchased from local market, upper Egypt	–	Yes	Yes-gas chromatography–mass spectrometry (GC–MS) analysis
Katiki et al. (2019)	Anethole and carvone	Appalachian farming systems research left	–	Yes	No
Lone et al. (2012)	*Euphorbia helioscopia* L	Kashmir valley, India	+	No	No
Lopes et al. (2018)	*Anacardium occidentale* L	NatVita in eusébio, ceará	–	Yes	Yes-liquid Chromatography-Mass spectroscopy (LC-MS) analysis
Maphosa et al. (2010)	*Elephantorrhiza elephantina* (Burch.) Skeels *Aloe ferox* Mill. *Leonotis leonurus* (L.) R. Br	Ntselamanzi, nkonkobe muncipality, eastern cape province, South Africa	+	Yes	No
Marie-Magdeleine et al. (2014)	*Musa x paradisiaca* L	Guadeloupe French west indies	–	No	No
Minho et al. (2008)	*Acacia decurrens* (J.C.Wendl.) Willd. (=*Acacia molissima* Willd.)	Not stated	–	Yes	No
Monteiro et al. (2011)	*Jatropha curcas* L	Obtained from embrapa eastern amazon, don eliseu	+	Yes	No
Njoku and Asuzu (1998)	*Ocimum gratissimum* L	Collected from nsukka in enugu state Nigeria	+	Yes	No
Nsereko et al. (2019)	*Senna occidentalis* (L.) Link. (=*Cassia occidentalis* L.) *Euphorbia hirta* L	Uganda	+	Yes	No
Oliveira et al. (2009)	*Cocos nucifera* L	Agroindustria tropical located in fortaleza, ceara state university	-	Yes	No
Ademola and Eloff (2011)	*Senna alata* (L.) Roxb. (=*Cassia alata*)	Collected from zaria, Nigeria	+	No	No
Martínez-Ortiz-de-Montellano et al. (2019)	*Lysiloma latisiliquum* (L.) Benth. *Onobrychis viciifolia* Scop	Harvested from tropical forest in merida, yucatan, Mexico	–	Yes	No
Pessoa et al. (2002)	*Ocimum gratissimum* L	Fortaleza, ceará, northeast of Brazil	+	Yes	Yes-method not stated
Iqbal et al. (2006b)	*Nicotiana tabacum* L	Purchased from local market in faisalabad, Pakistan	+	Yes	No
Sirama et al. (2015)	*Gymnanthemum amygdalinum* (Delile) Sch.Bip. (=*Vernonia amygdalina* Del.)	Not stated	–	Yes	No
Squires et al. (2010)	*Artemisia annua* L *Artemisia absinthium* L	Appalachian farming systems research left	–	No	No
Maphosa and Masika (2012)	*Elephantorrhiza elephantina* (Burch.) Skeels	Matatiele district, eastern cape province, South Africa	–	Yes	No
Maciel et al. (2006)	*Azadirachta indica* A. Juss. (=*Melia azedarach* L.)	Not stated	–	Yes	No
Macedo et al. (2010)	*Eucalyptus staigeriana* F. Muell. Ex F.M. Bailey	Dierberguer óleos essenciais ltda (barra bonita, são paulo state, Brazil	–	Yes	Yes-GC-MS analysis
Lone et al. (2013)	*Euphorbia helioscopia* L	Kashmir valley, India	+	No	No
Kamaraj et al. (2010)	*Azadirachta indica* A. Juss. (=*Melia azedarach* L.)	Amman nagar, dharamapuri district, Tamil nadu, India	+	Yes	No
Iqbal et al. (2006c)	*Swertia chirayita* (Roxb.) H.Karst. (=*Swertia chirata* Buch-Ham)	Procured from local market faisalabad, Pakistan	+	Yes	No
Zhu et al. (2013b)	*Artemisia lancea* Vaniot	Collected from hunan, China	+	Yes	Yes-GC-MS analysis
Idris et al. (1982)	*Artemisia herba-alba* Asso (=*Seriphidium herba-alba* (Asso) Soják)	Not stated	–	Yes	No
Silva et al. (2019)	*Parkia platycephala* Benth	Chapadinha, maranhao, Brazil	–	Yes	No

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TABLE 1 | (*Continued*) Quality assessment of the articles selected for this systematic review.

Study	Species/compound stated in the article	Plant source	Authenticated species	Quality control reported?	Chemical analysis reported?
Qi et al. (2015)	*Zanthoxylum bungeanum* Maxim. (=*Zanthoxylum simulans* Hance)	Collected from hunan, China	+	No	Yes-GC–MS analysis
Katiki et al. (2017b)	Essential oils and other compounds	Grasp Ind. Com. Ltda (curitiba, parana, Brazil)	–	No	Yes-gas chromatography (GC) analysis
Katiki et al. (2017a)	*Terminalia catappa* L	Instituto de zootecnia-nova odessa, sao polo, Brazil	+	Yes	Yes-method not stated
Ferreira et al. (2013)	*Annona muricata* L	Collected from terra de ismael grange located in the municipality of jurucê São paulo, Brazil	–	No	Yes-high performance liquid chromatography and (HPLC) thin-layer chromatography (TLC) analysis
Váradyová et al. (2018)	*Althaea officinalis* L *Petasites hybridus* (L.) G.Gaertn., B.Mey. and Scherb *Inula helenium* L *Malva sylvestris* L *Foeniculum vulgare* Mill. *Solidago virgaurea* L *Fumaria officinalis* L *Hyssopus officinalis* L *Melisa officinalis* L *Artemisia absinthium* L	Commercial sources (AGROKARPATY, plavnica, Slovak republic and BYLINY mikeš s.r.o., cíčenice, Czech republic)	–	No	Yes-liquid chromatography-Mass spectrometry assay
Vargas-Magaña et al. (2014)	*Lysiloma latisiliqum* (L.) Benth. *Laguncularia racemose* (L.) C.F. Gaertn *Rhizophora mangle* L *Avicenna germinans* (L.) L	Faculty of veterinary Medicine-UADY, in mérida, méxico collected from nearby coastal area of mérida, méxico	–	No	No
Mondal et al. (2015)	*Alternanthera sessilis* (L.) R.Br. ex DC.	Gopalgonj, Bangladesh	+	No	Yes-HPLC
Al-Shaibani et al. (2008)	*Justicia adhatoda* L. (=*Adhatoda vasica* Nees)	Harvested from sindh agriculture university (SAU), tandojam, Pakistan	+	Yes	No
Hussien et al. (2011)	*Corriandrum sativum* L *Thymus schimperi* Ronniger *Ocimum gratissimum* L *Ocimum lamiifolium* Hochst. ex Benth *Ruta chalepensis* L *Echinops kebericho* Mesfin	Collected from jimma town and also purchased from local market	+	No	No
Monglo et al. (2006)	*Annona senegalensis* Pers *Terminalia leiocarpa* (DC.) Baill. (=*Anogeissus leiocarpus* (DC) Guil and Perrot.) *Lippia rugosa* A.Chev *Stereospermum kunthianum* Cham. *Vernonia noveboracensis* (L.) Michx. (=*Vernonia tonoteana* L.)	Northern region of Cameroon	+	Yes	No
Ahmed et al. (2020)	*Artemisia herba-alba* Asso (=*Seriphidium herba-alba* (Asso) Soják) *Punica granatum* L	Midaga-tola district	+	No	Yes-method not stated

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TABLE 1 | (*Continued*) Quality assessment of the articles selected for this systematic review.

Study	Species/compound stated in the article	Plant source	Authenticated species	Quality control reported?	Chemical analysis reported?
Acharya et al. (2014)	*Rhus aromatica* Aiton *Ericameria nauseosa* (Pursh) G.L. Nesom and G.I. Baird *Perideridia gairdneri* (Hook. and Arn.) Mathias *Chrysothamnus viscidiflorus* Nutt. *Geranium viscosissimum* Fisch. and C.A. Mey *Melilotus albus* Medik *Liatris punctata* Hook. *Melilotus officinalis* (L.) Lam. *Sanguinaria canadensis* L *Lotus corniculatus* L *Arctostaphylos uva-ursi* (L.) Spreng *Rhus glabra* L *Wyethia sagittata* (Pursh) Mabb (=*Balsamorhiza sagittata* (Pursh) Nutt.) *Enothera* sp *Caltha palustris* L *Cynoglossum officinale* L *Solidago canadensis* L. (=*Solidago mollis* Bartl.) *Centaurea stoebe* L *Glycyrrhiza lepidota* Pursh *Lycopus americanus* Muhl. Ex W.P.C. Barton *Pedicularis racemose* Douglas ex Benth. *Stachys palustris* L *Agastache foeniculum* (Pursh) Kuntze *Pediomelum argophyllum* (Pursh.) J.W.Grimes *Monarda fistulosa* L *Clematis ligusticifolia* Nutt. *Allium cernuum* Roth *Erigeron canadensis* L. (=*Conyza canadensis* (L.) Cronquist) *Cornus Sericea* L *Rubus idaeus* L *Actaea rubra* (Aiton) Willd. *Symphoricarpos occidentalis* (R.Br.) Hook *Artemisia ludoviciana* Nutt. *Artemisia frigida* Willd. *Tanacetum vulgare* L *Cleomella serrulata* (Pursh) Roalson and J.C.Hall (=*Cleome serrulata* Pursh) *Epilobium angustifolium* L *Quercus macrocarpa* Michx. *Salix interior* Rowlee (=*Salix exigua* Nutt.) *Lithospermum molle* (Michx.) Muhl (=*Onosmodium molle* Michx.)	Collected from South Dakota, North Dakota, Wyoming Montana	+	No	No
Cavalcante et al. (2016)	*Calotropis procera* (Aiton.) W.T.Aiton	Universidade estadual do ceará	+	No	Yes-method not stated

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TABLE 1 | (*Continued*) Quality assessment of the articles selected for this systematic review.

Study	Species/compound stated in the article	Plant source	Authenticated species	Quality control reported?	Chemical analysis reported?
Ferreira et al. (2018)	*Citrus × aurantiifolia* (Christm.) Swingle *Anthemis nobilis* L. *Lavandula angustifolia* subsp. *angustifolia* (=*Lavandula officinalis* Chaix)	Purchased from kampo de ervas Ind. and com. Ltda-ME (ribeirão preto, SP, Brazil)	+	Yes	Yes-GC-MS
Fouche et al. (2016)	*Aloe rupestris* Baker *Antizoma angustifolia* (Burch.) Miers ex Harv. *Calpurnia aurea* (Aiton) Benth. *Senna italica* Mill. *Cissus quadrangularis* L *Clematis brachiata* Thunb. *Cleome gynandra* L *Ficus sycomorus* L *Hypoxis rigidula* Baker *Maerua angolensis* DC. *Monsonia angustifolia* E. Mey. Ex A.Rich *Pelargonium luridum* (Andrews) Sweet *Schkuhria pinnata* (lam.) Kuntze ex Thell. *Sclerocarya birrea* (A.Rich.) Hochst *Tabernaemontana elegans* Stapf	Collected from different locations in South Africa	+	No	No
Ahmed et al. (2013)	*Allium sativum* L *Aloe ferox* Mill *Ananas comosus* (L.) Merr. *Carica papaya* L *Ficus benjamina* L *Ficus ingens* (miq.) Miq *Ficus carica* L *Ficus benghalensis* L. (=*Ficus indica* L.) *Ficus lutea* Vahl *Ficus elastica* Roxb. Ex Hornem *Ficus natalensis* Hochst *Ficus sur* Forssk *Ficus sycomorus* L *Leonotis leonurus* (L.) R.Br *Azadirachta indica* A. Juss. (=*Melia azedarach* L.) *Peltophorum africanum* Sond *Scadoxus puniceus* (L.) Friis and Nordal *Lespedeza cuneata* (Dum. Cours.) G. Don *Tephrosia inandensis* H.M.L. Forbes *Warburgia ugandensis* v *Warburgia salutaris* (G. Bertol.) Chiov. *Cucumis myriocarpus* Naudin *Zingiber officinale* Roscoe	Collected from the university of KwaZulu-Natal (UKZN) botanical garden, pietermaritzburg campus, UKZN research farm (ukulinga). *Ficus* spp. were from a private garden (pietermaritzburg) and garlic and ginger samples were purchased from a commercial supermarket.	+	No	No
Iqbal et al. (2001b)	*Allium sativum* L *Zingiber officinale* Roscoe *Cucurbita ficifolia* Bouché (=*Curcurbita mexicana* Dammann) *Ficus religiosa* L	Not stated	-	No	No

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TABLE 1 | (*Continued*) Quality assessment of the articles selected for this systematic review.

Study	Species/compound stated in the article	Plant source	Authenticated species	Quality control reported?	Chemical analysis reported?
Getachew et al. (2012)	*Foeniculum vulgare* Mill *Acokanthera schimperi* (A.DC.) Schweinf *Searsia pyroides* (Burch.) Moffett (=*Rhus vulgaris* Meikle) *Rhus glabra* L *Jasminum abyssinicum* Hochst. ex DC. *Myrsine africana* L	Collected from addis ababa	+	No	No
Zamilpa et al. (2019)	*Dysphania ambrosioides* (L.) Mosyakin and Clemants (=*Chenopodium ambrosioides* L.) *Castela tortuosa* Liebm	Acquired at a local market in the town left of cuernavaca city, morelos, Mexico	+	Yes	No
Iqbal et al. (2005)	*Calotropis procera* (Aiton) W.T.Aiton	Cholistan rangeland, district bahawalpur (Pakistan)	+	Yes	No
Jabbar et al. (2007)	*Chenopodium album* L *Caesalpinia crista* L	Procured from local market in faisalabad (Pakistan)	+	No	No
Kamaraj and Rahuman (2011)	*Annona squamosa* L *Eclipta prostrata* (L.) L *Solanum torvum* Sw *Terminalia chebula* Retz *Catharanthus roseus* (L.) G. Don	Collected from the tropical region hills, Tamil nadu, India	+	No	Yes-lieberman–Burchard test
Kamaraj et al. (2011)	*Andrographis paniculata* (Burm.f.) Nees *Anisomeles malabarica* (L.) Kuntze (=*Anisomeles malabarica* (L.) R.Br.) *Annona squamosa* L *Datura metel* L *Solanum torvum* Sw	Collected from javadhu hills, tiruvannamalai district and dharmapuri district Tamil nadu, India	-	Yes	No
Marie-Magdeleine et al. (2010)	*Tabernaemontana citrifolia* L	Collected in Guadeloupe, French west indies	-	No	Yes-TLC
Nery et al. (2010)	*Anacardium humile* A.St.-Hil	Collected in the cerrado of a rural region of montes claros city, Brazil	+	No	Yes-phytochemical analysis
Veerakumari and Chitra (2016)	*Allium sativum* L	Not stated	-	Yes	No
de Oliveira et al. (2011)	*Myracrodruon urundeuva* Allemao	Collected in December 2009 in fortaleza, Ceará,Brazil	+	Yes	Yes-method not stated
Malik et al. (2019)	*Artemisia vulgaris* L	Collected from botanical garden at the federal university of maranhão, sao luís, maranhão, Brazil	+	No	Yes-GC-MS analysis
Soares et al. (2018)	*Myracrodruon urundeuva* Allemao	Purchased from arboleft seed trade (birigui, sao paulo, Brazil)	+	No	Yes-proteomic analysis (LC-ESI-MS/MS)
Tariq et al. (2009)	*Artemisia absinthium* L	Collected from the aharbal area of southern kashmir valley	+	No	No
Zhu et al. (2013a)	*Arisaema franchetianum* Engl. *Arisaema lobatum* Engl.	Collected from yunnan province, China	+	No	Yes-GC–MS analysis
Carvalho et al. (2012)	*Lippia origanoides* Kunth (=*Lippia sidoides* Cham.) *Mentha* × *piperita* L *Hura crepitans* L *Couroupita guianensis* Aubl.	Institute of chemistry of paulista state Embrapa western. Amazon research station, Brazil Acquired in the local market of porto velho	-	No	Yes- GC-MS analysis
Katiki et al. (2012)	*Cymbopogon schoenanthus* (L.) Spreng	Purchased from WNF Ind. and com. Ltda (sao Paulo-SP, Brazil)	-	No	Yes- GC analysis

TABLE 1 | (*Continued*) Quality assessment of the articles selected for this systematic review.

| Study	Species/compound stated in the article	Plant source	Authenticated species	Quality control reported?	Chemical analysis reported?
Macedo et al. (2012)	*Lantana camara* L *Alpinia zerumbet* (Pers.) B.L.Burtt and R.M.Sm *Mentha arvensis* L. (=*Mentha villosa* Becker) *Tagetes minuta* L	Collected in the horto of medicinal plants of the universidade federal do ceará in plots, state of ceará, Brazil	+	No	Yes-GC analysis
Ribeiro et al. (2014)	*Corymbia citriodora* (Hook.) K.D.Hill and L.A.S.Johnson (=*Eucalyptus citriodora* Hook.)	Purchased from FERQUIMA (vargem grande paulista, são paulo, Brazil)	-	No	Yes- infrared spectroscopy (FTIR)
Andre et al. (2016)	Carvacrol	Obtained via the acetylation of carvacrol (Sigma–Aldrich®, st. Louis, United States	-	No	Yes-FTIR
Morais-Costa et al. (2016)	*Lachesiodendron viridiflorum* (Kunth) P.G.Ribeiro, L.P.Queiroz and Luckow (=*Piptadenia viridiflora* (Kunth) Benth.)	Cerrado vegetationnear montes claros city in north minas gerais state, Brazil	-	Yes	Yes-HPLC-DAD
Féboli et al. (2016)	*Opuntia ficus-indica* (L.) Mill.	Collected in the municipality of ilha solteirain the state of são paulo, Brazil in September 2014	-	No	No
Tadesse et al. (2009)	*Maesa lanceolate* Forssk *Coleus maculosus* subsp. Maculosus (=*Plectranthus punctatus* (L.f.) L'Her.)	Collected along the addis ababa-butajira road and *Maesa laceolata*	+	No	No
Herath et al. (2019)	*Cryptocarya massoy* (Oken) Kosterm. (=*Cryptocarya ovoguineensis* Teschner) *Piper methysticum* G.Forst	Not stated	-	Yes	Yes-HPLC
Gaínza et al. (2015)	*Citrus × aurantium* L. (=*Citrus × sinensis* (L.) Osbeck) *Melaleuca quinquenervia* (Cav.) S.T.Blake	Not stated	–	Yes	Yes-GC–MS analysis
de Araújo-Filho et al. (2018)	*Corymbia citriodora* (Hook.) K.D.Hill and L.A.S.Johnson (=*Eucalyptus citriodora* hook.)	Purchased from ferquima (são paulo, Brazil)	–	Yes	Yes-GC–MS analysis
Hördegen et al. (2006)	*Azadirachta indica* A. Juss *Caesalpinia crista* L *Fumaria parviflora* Lam *Embelia ribes* Burm. f *Baccharoides anthelmintica* (L.) Moench (=*Vernonia anthelmintica* (L.) Willd.) *Ananas comosus* (L.) Merr.	Obtained from alfred galke GmbH, gittelde (Germany). Purchased from S.V.S. Medicinal crops dealers pvt. Ltd., guntur (India)	–	No	No
Camurça-Vasconcelos et al. (2007)	*Croton grewioides* Baill. (=*Croton zehntneri* Pax and K.Hoffm.) *Lippia origanoides* Kunth. (=*Lippia sidoides* Cham.)	Collected in vicosa, ceara state, Brazil Purchased from PRONAT (produtos naturais) in the state of ceara	+	No	Yes-GC–MS analysis
Hernández-Villegas et al. (2011)	*Phytolacca icosandra* L	Collected in yaxcabá, yucatan, Mexico	+	No	Yes-method not stated

TABLE 1 | (*Continued*) Quality assessment of the articles selected for this systematic review.

Study	Species/compound stated in the article	Plant source	Authenticated species	Quality control reported?	Chemical analysis reported?
Eguale et al. (2011)	*Croton macrostachyus* Hochst. ex Delile *Ekebergia capensis* Sparrm. *Vachellia nilotica* (L.) P.J.H.Hurter and Mabb. (=*Acacia nilotica* (L.) willd. Ex. Delile) *Terminalia schimperiana* Hochst. (=*Terminalia glaucescens* Planch. ex Benth.)	Collected from their natural habitat	+	No	Yes-method not stated
Hamad et al. (2014)	*Nicotiana tabacum* L *Azadirachta indica* A. Juss	Purchased from the local market of faisalabad, Pakistan	–	Yes	No
De Jesús-Gabino et al. (2010)	*Prosopis laevigata* (Humb. and Bonpl. Ex Willd.) M.C.Johnst	Collected from the sierra de huautla, ecological reserve of the biosphere, in morelos state, Mexico	–	No	No
Tariq et al. (2008)	*Achillea millefolium* L	Collected from the aharbal area of southern kashmir valley	+	No	No
Piza et al. (2019)	*Psidium cattleyanum* Sabine	Glaucilândia, Brazil	+	Yes	No
André et al. (2020)	Carvacryl acetate	Not stated	–	Yes	Yes-GC- MS analysis
Macedo et al. (2019)	*Cymbopogon citratus* (DC.) Stapf	Not stated	–	Yes	Yes-GC-MS analysis
Araújo-Filho et al. (2019)	*Corymbia citriodora* (Hook.) K.D.Hill and L.A.S.Johnson (=*Eucalyptus citriodora* Hook.)	Not stated	–	Yes	Yes-GC-MS analysis
Iqbal et al. (2001a)	*Sorghum bicolor* (L.) Moench	Not stated	–	Yes	No
Lara TF et al. (2009)	*Eucalyptus globulus* Labill.	Not stated	–	Yes	Yes-GC-MS analysis
Ademola et al. (2004)	*Khaya senegalensis* (Desv.) A. Juss	Ibadan, Nigeria	+	Yes	No
Ademola et al. (2007)	*Spigelia anthelmia* L	Ibadan, Nigeria	+	Yes	No
Alowanou et al. (2019)	*Bridelia ferruginea* Benth *Combretum glutinosum* Perr. ExDC. *Mitragyna inermis* (Willd.) Kuntz	Abomey-calavi, kandi and comé, Benin	+	Yes	No
Al-Qarawi et al. (2001)	*Calotropis procera* (Aiton.) W.T.Aiton	Purchased from local market in almoznib, king saud university at buraydah	–	Yes	No
Iqbal et al. (2006a)	*Baccharoides anthelmintica* (L.) Moench (=*Vernonia anthelmintica* (L.) Willd.)	Faisalabad, Punjab	+	Yes	No
Ademola and Idowu (2006)	*Leucaena leocochephala* (Lam.) de Wit	Ibadan, Nigeria	+	Yes	No
Barone et al. (2018)	*Vaccinium macrocarpon* Aiton	Not stated	–	Yes	Yes-Mass spectra method
Castillo-Mitre et al. (2017)	*Vachellia campeachiana* (Mill.) Seigler and Ebinger (=*Acacia cochliacantha* humb. and bonpl. Ex willd.)	Salitre palmarillos village, Mexico	+	Yes	Yes-Mass spectrometry and HPLC analysis
Domingues et al. (2013)	*Ananas comosus* (L.) Merr.	São paulo state, Brazil	+	Yes	No
Dixit et al. (2019)	*Annona squamosa* L *Azadirachta indica* A. Juss *Nicotiana tabacum* L	Local market, jabalpur India	–	Yes	No
Ferreira et al. (2016)	*Thymus vulgaris* L	Ferquima Ind e com ltda (Brazil)	+	Yes	Yes-GC-MS analysis
Githiori et al. (2004)	*Hagenia abyssinica* (Bruce) J.F.Gmel *Dodonaea viscosa* subsp. *angustifolia* (L.f.) J.G.West (=*Dodonaea angustifolia* L.f.) *Olea europaea* L *Annona squamosa* L *Hildebrandtia sepalosa* Rendle *Azadirachta indica* A. Juss *Ananas comosus* (L.) Merr.	Kenya and east africa	–	Yes	No

(Continued on following page)

TABLE 1 | (*Continued*) Quality assessment of the articles selected for this systematic review.

Study	Species/compound stated in the article	Plant source	Authenticated species	Quality control reported?	Chemical analysis reported?
Heckendorn et al. (2006)	*Onobrychis viciifolia* Scop	Not stated	−	Yes	No
Palacios-Landín et al. (2015)	*Allium sativum* L *Tagetes erecta* L	Local market of the city of cuernavaca and rural area of tixtla in the state of morelos, Mexico	−	Yes	No
Hassan et al. (2019)	*Abutilon theophrasti* Medik	"Lower-munda" District, Qazigund,India	+	Yes	No
Iqbal et al. (2004)	*Seriphidium brevifolium* (Wall. ex DC.) Ling and Y.R.Ling (=*Artemisia brevifolia* Wall. ex. DC.)	Faisalabad, Pakistan	+	Yes	No
Cabardo and Portugaliza (2017)	*Moringa oleifera* Lam	Collected from brgy. Sto. Rosario, baybay city, leyte	-	No	No
Assis et al. (2003)	*Spigelia anthelmia* L	Not stated	−	No	No
Hajaji et al. (2018)	*Matricaria recutita* L	Obtained from beja, north-west of tunitia	−	Yes	Yes-method not stated
Costa et al. (2008)	*Azadirachta indica* A. Juss	Collected in eusebio, ceara, located in northeast Brazil	+	No	Yes-method not stated
Cortes-Morales et al. (2019)	*Baccharis conferta* Kunth	Collected from the iztaccíhuatl-popocatépetl national park	+	Yes	Yes-TLC
Eguale et al. (2007a)	*Hedera helix* L	Collected from addis ababa, Ethiopia	+	Yes	Yes-method not stated
Eguale et al. (2007b)	*Coriandrum sativum* L	Purchased from debre birhan, Ethiopia	+	Yes	Yes-method not stated
Oliveira et al. (2014)	*Piper aduncum* L	Galley forest of the angico river, bocaiúva site, minas gerais state, Brazil	+	Yes	Yes-GC analysis
Karim et al. (2019)	*Artemisia vulgaris* L	BAU campus	−	Yes	No

FIGURE 2 | Selection and processing of plant material(s) for anthelmintic evaluation.
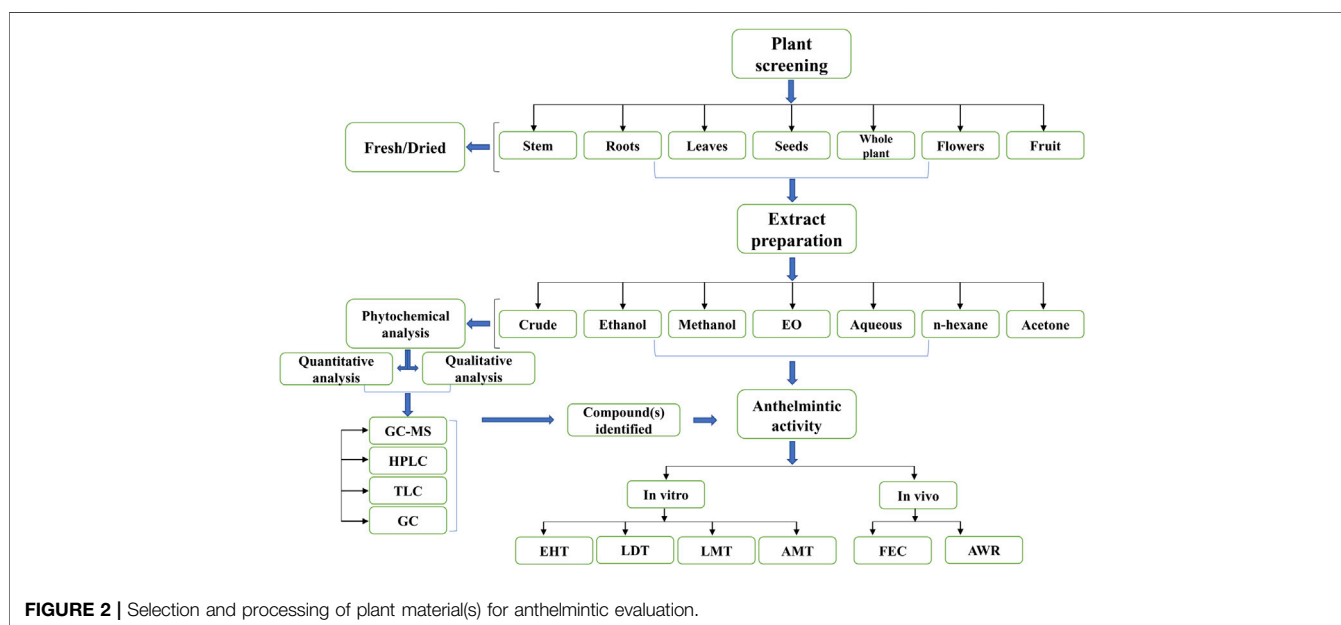
frequently used part (50%) followed by seeds (11.3%), roots (8%), and whole plants (7%). Among other plant parts stems, flowers, barks, shoots, fruits, bulbs, peel, fibers, pulp, and latex were included (**Supplementary Table S2**).

Different solvents including n-hexane, aqueous, ethanolic, hydro-alcoholic, methanolic, and others were used in extracts preparation (**Figure 2**). Among all, the methanol extract was the predominant one. Bioassays reported in this review included, egg
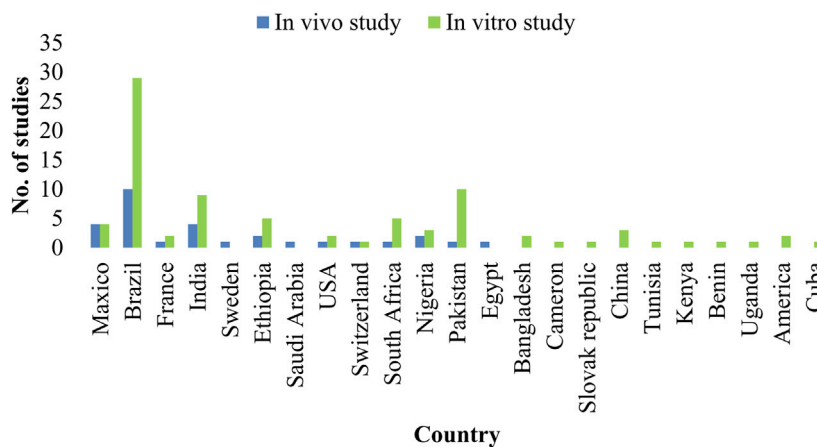
FIGURE 3 | Country-wise comparison of *in vitro* and *in vivo* studies.
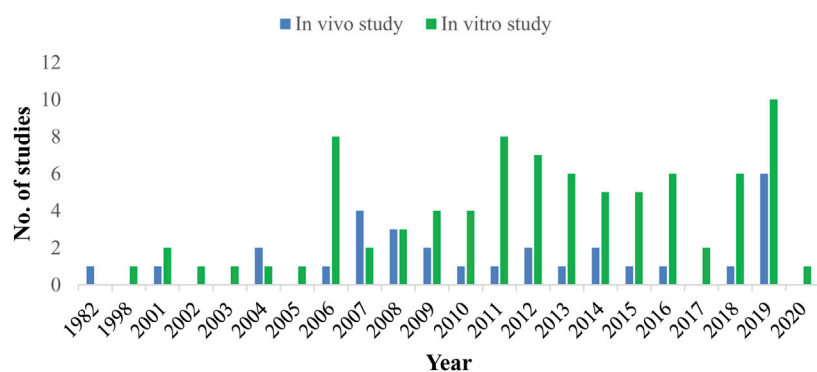

FIGURE 4 | Year-wise comparison of *in vitro* and *in vivo* studies.

hatching test (EHT), larval development test (LDT), larval motility test (LMT), adult worm motility test (AWMT), adult parasite mortality test (APMT), and larval artificial exsheathment assay (LAEA) in *in vitro* studies, while fecal egg count reduction (FECR), egg count per gram of feces (EPG), total warm count reduction (TWC/WCR) in *in vivo* studies. Furthermore, among the above mentioned assays, EHT was the most widely used assay for evaluation of medicinal plants against *H. contortus in vitro*, while FECR was common *in vivo*. Sheep were the commonly used experimental model *in vivo* (**Supplementary Table S3**).

Out of the total reported plant species 171 plant species were evaluated *in vitro* and only 40 plant species *in vivo* against *H. contortus*. It is evident that *in vitro* studies were almost five times greater than *in vivo* studies. Mostly, *in vitro* studies were carried out in Brazil (*n* = 29 studies), then in Pakistan (*n* = 10 studies), and India (*n* = 9 studies) among others. Similarly, *in vivo* studies were also mostly reported

from Brazil and India, 10 and 4 studies, respectively, (**Figure 3**). Most of the pharmacological studies were reported in the year 2019 (*n* = 15) and 2006, 2011, 2012 (*n* = 9) in each (**Figure 4**).

Comparative Analysis and Toxicity of Common Plant Species

Plant species, which were common in both *in vitro* and *in vivo* studies, were compared to discriminate their efficacy against *H. contortus*. A total of 24 plant species were found to be commonly used both *in vitro* and *in vivo* (**Table 2**).

After comparative analysis based on minimum concentration and maximum efficacy, the identified plant species with promising anthelmintic activity *in vitro* against *H. contortus* were *Lachesiodendron viridiflorum* (Kunth) P.G.Ribeiro, L.P.Queiroz and Luckow (syn. *Piptadenia viridiflora* (Kunth) Benth.), *Cymbopogon schoenanthus* (L.) Spreng., *Allium*

TABLE 2 | Comparative analysis, toxicology, and mechanism of action of medicinal plants.

Plant names	*In vitro*			*In vivo*			Toxicology		Mechanism of action	References
	Ext	Conc. (mg/ml)	Eff. (%)	Ext	Dos. (mg/kg)	Eff. (%)	Dos. (mg/kg)	T. level		
Allium sativum L	Ethanol	0.5	88.5–100	n-hexane	40	68.7	NA	Moderate	Destructive and inhibitive effect on acetylcholinesterase causing paralysis	Krstin et al. (2018); Palacios-Landín et al. (2015); Veerakumari and Chitra (2016)
Annona squamosa L	Methanol	25	100	Aqueous	1500	No effect	NA	NA	NA	Dixit et al. (2019); Kamaraj et al. (2011)
Achillea millefolium L	Crude aqueous	25	94.4	Crude aqueous	2	88.4	0.01 0.003	Nil	Alteration of cell shape, restrict growth, collapsing cell membrane, and arrest cell division	Cavalcanti et al. (2006); Tariq et al. (2008)
Artemisia absinthium L	Methanol	1.024 25	100 85	Crude ethanol	2000	90.46	NA	Toxic	Inhibit vital metabolic enzymes, disrupt mitochondrial membrane potential, release of cytochrome c into cytoplasm and activation of caspase-3-mediated apoptosis	Lachenmeier (2010); Tariq et al. (2009); Váradyová et al. (2018)
Artemisia herba-alba Asso	Methanol	1.25–10	100	NA	0.003	100	300	Toxic	NA	Ahmed et al. (2020); Almasad et al. (2007); Idris et al. (1982)
Artemisia capillaris Thunb. (=*Artemisia vestita* Wall. ex Besser)	Methanol	50 25	95 100	Methanol	50	86.35	NA	Nil	NA	Irum et al. (2015)
Artemisia maritima L. (=*Seriphidium maritimum* (L.) Poljakov	Methanol	25	100	Methanol	50	82.22	NA	Nil	NA	Irum et al. (2015)
Ananas comosus (L.) Merr.	Ethanol	200	100	Aqueous	2000	No effect	750 5000	Nil	Remove and digest the cuticle layer causing immobility and death	Ahmed et al. (2013); Domingues et al. (2013); Maurer (2001)
Azadirachta indica A. Juss	Aqueous Hydro-alcoholic Ethanol	12.5 12.5 50	97.8 98.4 100	Aqueous Methanol	4000	85.24	18.4–45	Toxic	Inhibit secretion of key enzymes, intracellular instability, neuromuscular disorganization, paralysis, and death	Deng et al. (2013); Hamad et al. (2014); Kamaraj et al. (2010); Maciel et al. (2006)
Calotropis procera (Aiton) W.T.Aiton	Aqueous Ethyl acetate	25 4	70 91	Aqueous	0.003	88.4	0.001–6	Toxic	Tegumental disorganization and paralysis	Cavalcante et al. (2016); Iqbal et al. (2005); Mahmoud et al. (1979)
Castela tortuosa Liebm.	n-hexane	40	70	n-hexane	40	27.1	NA	NA	NA	(Zamilpa et al., 2019)
Coriandrum sativum L	Essential oil	10	88.63	Aqueous	450	25	1000–5000	Nil	Inhibit vital functions, interfere metabolic processes, and destruction of nervous system	Eguale et al. (2007b); Hussien et al. (2011); Patel et al. (2012)
Cocos nucifera L	Ethyl acetate	5 80	100 99.77	Ethyl acetate	400	Not effective	2000	Toxic	Induces chemical and physical damage by binding to proteins of cuticle, oral cavity, esophagus, and cloaca	Oliveira et al. (2009); Tayler et al. (2020)
Corymbia citriodora (Hook.) K.D.Hill and L.A.S. Johnson	Essential oil	2 8	100 100	Essential oil	0.125, 0.25, 0.5	100	5000	Moderate	Formation of vacuoles, muscular disorganization, and changes in mitochondrial profile	Araújo-Filho et al. (2019); Ribeiro et al. (2014)
Cymbopogon citratus (DC.) Stapf	Essential oil Essential oil nano-emulsion	1.25	98.4 97.1	Essential oil	50	23.9	31.2 µg/ml	Nil	Alter the permeability, depolarization of membrane, and disrupt lipids, polysaccharides, and phospholipids	Macedo et al. (2019); Santoro et al. (2007)

TABLE 2 | (*Continued*) Comparative analysis, toxicology, and mechanism of action of medicinal plants.

Plant names	In vitro			In vivo			Toxicology		Mechanism of action	References
	Ext	Conc. (mg/ml)	Eff. (%)	Ext	Dos. (mg/kg)	Eff. (%)	Dos. (mg/kg)	T. level		
Cymbopogon schoenanthus (L.) Spreng.	Essential oil	0.18	98.6 96.8	Essential oil	360	No activity	180; 360	Nil	Inhibit vital functions, interfere metabolic processes, and destruction of nervous system	Katiki et al. (2012)
Eucalyptus staigeriana F. Muell. Ex F.M. Bailey	Essential oil	1.75	100	Essential oil	500	46.44	1000–5000 200–600	Nil	Alter the permeability, depolarization of membrane, and disrupt lipids, polysaccharides, and phospholipids	Macedo et al. (2010); Ribeiro et al. (2014)
Euphorbia helioscopia L	Methanol	25	98 82	Methanol	5	86	2000	Nil	Induce expansion, increase permeability, and disturb chemical structure of membrane	Lone et al. (2012); Saleem et al. (2016)
Lippia origanoides Kunth (=*Lippia sidoides* cham.)	Essential oil	0.625	100	Essential oil	283	56.9	NA	Moderate	Inhibit vital functions, interfere metabolic processes, nervous system destruction	Camurça-Vasconcelos et al. (2007); de Melo et al. (2020)
Lysiloma latisiliquum (L.) Benth.	Acetone	3.6	Not effective	NA	0.8	Highly effective	NA	NA	Cytoplasmic vacuolization, disturb muscular cells, and tissues	Martínez-Ortiz-de-Montellano et al. (2019); Vargas-Magaña et al. (2014)
Nicotiana tabacum L	Aqueous Methanol	25	77	Aqueous Methano	4000	86.6	5000	Nil	Inhibit acetylcholine, and paralysis	Andjani et al. (2019); Hamad et al. (2014); Iqbal et al. (2006b)
Lachesiodendron viridiflorum (Kunth) P.G.Ribeiro, L.P.Queiroz and Luckow (=*Piptadenia viridiflora* (Kunth) Benth.)	Aqueous Methanol	0.075	100	Aqueous	283	Highly effective	203	Nil	Inhibit enzymatic activities and metabolic processes	Morais-Costa et al. (2016)
Seriphidium brevifolium (Wall. Ex DC.) Ling and Y.R.Ling	Methanol	25	80	Aqueous	0.003	67.2	NA	NA	NA	Iqbal et al. (2004)
Spigelia anthelmia L	Ethyl acetate Methanol	50	Highly effective	Aqueous	500	Significantly effective	5000	Nil	Destruct cuticle layer, degrade egg membrane and chitin of egg shell, inhibit development and death	Ademola et al. (2007); Assis et al. (2003); Ribeiro et al. (2017)

NA, Data not available.

sativum L., *Lippia origanoides* Kunth (syn. *Lippia sidoides* Chem.), *Artemisia absinthium* L., *Cymbopogon citratus* (DC.) Stapf, *Eucalyptus staigeriana* F. Muell. ex F.M. Bailey, *Artemisia herba-alba* Asso, and *Corymbia citriodora* (Hook.) K.D. Hill and L.A.S. Johnson in order of their appearance. While *A. herba-alba*, *C. procera*, *C. citriodora*, *Lysiloma latisiliqum* (L.) Benth., and *Euphorbia helioscopia* L. were reported with high efficacy *in vivo*. Among the plants, *L. viridiflorum* was found highly effective both *in vitro* and *in vivo* with no observed toxic effects. *C. citriodora* was moderately toxic *in vivo*, but with promising nematicidal activity *in vitro* and *in vivo*. Additionally, *C. procera* and *A. herba-alba* despite of their high anti-haemonchiasis activity were found to be highly toxic at the tested concentrations (**Supplementary Table S4**). However, five species namely; *Annona squamosa* L., *Artemisia maritima* L., *Artemisia capillaris* Thunb., *Castela tortuosa* Liebm., *L. latisiliquum*, and *Seriphidium brevifolium* (Wall. ex DC.) Ling and Y.R. Ling were not evaluated for their toxicological effects. Mostly non-toxic and low-toxic extracts were orally administered. The LC_{50} value of most plant species was missing and was not calculated.

From the results, it is evident that the effects of different plant extracts were dose and time dependent. Moreover, the comparative analysis also revealed that plant species were more effective *in vitro* than *in vivo* against various stages of the parasite.

Phyto-Compounds With Anti-Haemonchiasis Activity

In this review, 19 compounds were reported to be assessed for *in vitro* activity against different life stages of *H. contortus*. While only 3 compounds were found to be evaluated for *in vivo* activity using gerbil (*Meriones unguiculatus*) as an animal model. Based on minimum concentration and maximum nematicidal activity, Cinnamaldehyde, anethole, and carvone were highly active and completely inhibited egg hatching of the parasite at the tested concentrations of 0.085, 0.085, and 0.366 mg/ml, respectively. Carvacrol inhibited the larval development at a minimum concentration of 1 mg/ml, though the effectiveness of thymol and anethole against larvae development was also significant, but relatively at high concentrations i.e., 10 and 20 mg/ml, correspondingly.

Carvacrol and carvacryl acetate at 2 mg/ml showed 100% larval motility inhibition as compared to other compounds. Similarly, carvacryl acetate (0.2 mg/ml) and citronellal (2 mg/ml) totally reduced the motility of adult parasites *in vitro*. However, citronellal was moderately toxic in mice. Anethole and carvone significantly reduced fecal egg count, decreased male length, and reproductive capacity of female at 50 mg/kg concentration *in vivo* (**Table 3**).

Quantitative Analysis
Jaccard Similarity Index
The JI was used to compare the two sets of data (i.e., *in vitro* and *in vivo* studies) to determine the similarity of the studies reported in this review. The result revealed 12.8% similarity between the two data sets (**Figure 5**).

DISCUSSION

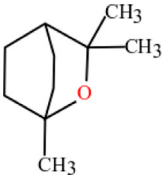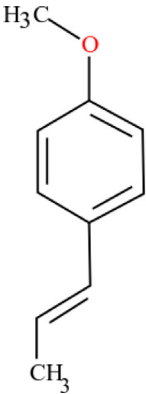## Anti-haemonchiasis Medicinal Plants, Their Families, and Habit

Extensive use of Asteraceae, Fabaceae, Lamiaceae, and Euphorbiaceae, users' reliability, and antiparasitic activity could be attributed to the presence of potent phytochemicals such as saponins, tannins, flavonoids in Asteraceae (Carvalho et al., 2013), saponins, essential oils in Lamiaceae (Raja, 2012), phenolic compounds, alkaloids, and hemagglutinins in Fabaceae (Żarnowski et al., 2001), and alkaloids and terpenoids in Euphorbiaceae (Mwine and Van Damme, 2011). Mechanism of action of these compounds against different developmental stages of *H. contortus* is still unknown, however, probably these may inhibit both egg embryonation and direct effects on the larvae (Al-Shaibani et al., 2008). Athanasiadou et al. (2001) attributed the antiparasitic activity of condensed tannins to their ability to bind with the cellular membrane proteins, which results in the unavailability of nutrients to the larvae, causing starvation, and death (Athanasiadou et al., 2001). It seems that complexities of these compounds enable them to interrupt various molecular targets of different developmental stages of the parasite. Saponoids usually act by binding to surface molecules (proteins/sterols) inducing inhibition of the protein expression, and/or lysis of the cell (Bruneton, 1993). The expression of surface proteins of nematodes is stage specific (Rhoads and Fetterer, 1994).

Furthermore, Asteraceae is being the first and Fabaceae is the third largest terrestrial plant families all over the world and this could be another possible reason for such an extensive utilization of these families (Tariq et al., 2017). Plant species of Fabaceae are able to fix nitrogen, which leads to protein deposition in leaves and seeds (Molares and Ladio, 2012). Species of Lamiaceae could be easily cultivated and propagated, moreover, they are mostly utilized due to their strong aroma and ability to survive in severe hot weather because of their essential oils (Raja, 2012). Euphorbiaceae extensive use for different medicinal purposes may be attributed to its global distribution and mode of adaptation in the worst dry conditions because of the succulent nature of its species and crassulacean acid metabolism (CAM) pathway ability. Plants of this family possess a wide array of secondary metabolites and tendency of mutation load due to their exposure to a wide range of environmental conditions (Mwine and Van Damme, 2011).

Herbs were frequently used form of life against *H. contortus* eggs, larvae, and adult worms as compared to trees and shrubs. The dominancy of herbs over other forms of life could be attributed to their easy availability and high efficacy against different ailments as compared to shrubs and trees (Ahmad et al., 2009). Herbs are widely used in folk medicines all over the globe and contain a large number of active compounds responsible for their high efficacy and, therefore, are preferred by the scientists and traditional healers (Tariq et al., 2017).
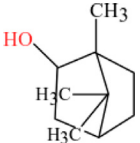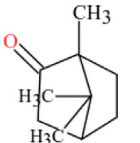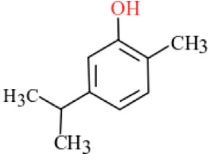
Leaves were reported as the widely used part during pharmacological validation of medicinal plants against *H. contortus*. Leaves contain a variety of chemical compounds

TABLE 3 | Plant compounds efficacy against *H. contortus*.

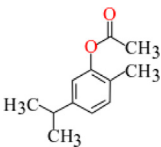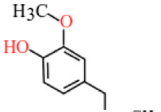| Compound name	IUPAC name	Chemical structure	Plant name/family	Extract	Concentration (mg/ml)	Assays	Inhibition (%)	References
1,8-Cineole	1,3,3-Trimethyl-2-oxabicyclo [2.2.2] octan		*Artemisia lancea* Vaniot/Asteraceae	Essential oil	0.63	EHT	3.4	Zhu et al. (2013b)
					1.25		10.0	
					2.5		26.6	
					5.0		56.6	
					10.0		74.8	
					0.63	LDT	10.6	
					1.25		23.4	
					2.5		33.6	
					5.0		49.2	
					10.0		65.2	
					0.63	LMT	5.5	
					1.25		10.4	
					2.5		30.2	
					5.0		48.6	
					10.0		60.3	
Anethole	1-Methoxy-4-(prop-1-en-1-yl)benzene		Produced synthetically	Essential oil	1,787	EHT	99	Katiki et al. (2017b)
			Croton zehntneri Pax and K.Hoffm./ Euphorbiaceae	Essential oil	0.31	EHT	6.7	Camurça-Vasconcelos et al. (2007)
					0.62		26.6	
					1.25		99.9	
					1.25	LDT	35.8	
					2.5		52.1	
					5.0		87.7	
					10.0		96.7	
					20.0		100	
			Supplied by GRASP Ind. E com. (Curitibia-PR, Brazil)	Encapsulated oil	50	FEC*	Fecal egg count was significantly reduced, decreased male length, and reproductive capacity of female after 45 days in santa ines lambs	Katiki et al. (2019)
					20		The dose did not affect acquisition of parasites after pasture access and as FEC raised and body weight decreased of morada nova lambs	
			Produced synthetically	Essential oil	0.085	EHT	99	Katiki et al. (2017b)

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Medicinal Plants Against *Haemonchus contortus*

TABLE 3 | (*Continued*) Plant compounds efficacy against *H. contortus*.

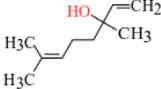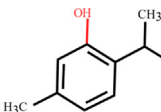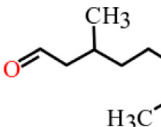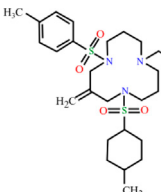| Compound name	IUPAC name	Chemical structure	Plant name/family	Extract	Concentration (mg/ml)	Assays	Inhibition (%)	References
Borneol	1,7,7-Trimethylbicyclo [2.2.1] heptan-2-ol		*Zanthoxylum bungeanum* Maxim. (=*Zanthoxylum simulans* Hance)/ Rutaceae	Essential oil	1.25	EHT	48.6	Qi et al. (2015)
					2.5		62.1	
					5.0		80.0	
					10.0		92.2	
					20.0		98.8	
					40.0		100	
					1.25	LDT	38.2	
					2.5		52.2	
					5.0		80.2	
					10.0		91.2	
					20.0		98.0	
					40.0		100	
					1.25	LMT	52.8	
					2.5		37.2	
					5.0		23.2	
					10.0		9.6	
					20.0		2.6	
					40.0		1.8	
Camphor	1,7,7-trimethylbicyclo [2.2.1] heptan-2-one		*Artemisia lancea* Vaniot/Asteraceae	Essential oil	0.63	EHT	-	Zhu et al. (2013b)
					1.25		-	
					2.5		2.8	
					5.0		9.0	
					10.0		12.8	
					0.63	LDT	4.4	
					1.25		15.8	
					2.5		23.4	
					5.0		37.2	
					10.0		57.0	
					0.63	LMT	5.7	
					1.25		13.2	
					2.5		17.4	
					5.0		13.0	
					10.0		18.1	
Carvacrol	2-Methyl-5-(propan-2-yl) phenol		*Arisaema franchetianum* Engl., *A. lobatum* Engl./Araceae	Essential oil	0.32	EHT	52.6	Zhu et al. (2013a)
					0.63		65.6	
					1.25		83.4	
					2.5		93.2	
					5.0		100	
					10.0		100	
					0.32	LDT	38.4	
					0.63		54.2	
					1.25		77.2	
					2.5		89.2	
					5.0		98.0	
					10.0		100	
		Produced synthetically		Essential oil	5.517	EHT	99	Katiki et al. (2017b)
				Essential oil	1	EHT	97.7	Andre et al. (2016)
					2	LMT	100	
					0.2	AWMT	58.3	
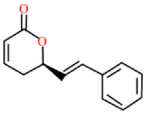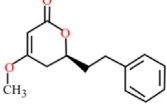
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TABLE 3 | (*Continued*) Plant compounds efficacy against *H. contortus*.

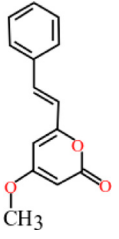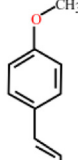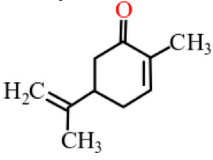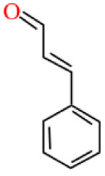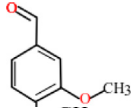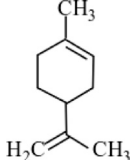| Compound name	IUPAC name	Chemical structure	Plant name/family	Extract	Concentration (mg/ml)	Assays	Inhibition (%)	References
Carvacryl acetate*	Phenol, 2-methyl-5-(1-Methylethyl)-, Acetate		NA	NA	250	EGP	The compound reduced 57.7% of eggs per Gram of gastrointestinal parasites including *H. contortus*	André et al. (2020)
				Essential oil	8	EHT	89.3	Andre et al. (2016)
					2	LMT	100	
					0.2	AWMT	100	
Eugenol	4-Allyl-2-methoxyphenol		*Ocimum gratissimum* L./Lamiaceae	Essential oil	0.625	EHT	58.49	Pessoa et al. (2002)
					1.25		76.02	
					2.5		94.56	
					5		100	
					10		100	
Linalool	3,7-Dimethyl-1,6-octadien-3-ol		Produced synthetically	Essential oil	51.65	EHT	99	Katiki et al. (2017b)
			Arisaema franchetianum Engl., *A. lobatum* Engl./Araceae	Essential oil	0.32	EHT	2.0	Zhu et al. (2013a)
					0.63		6.4	
					1.25		12.6	
					2.5		29.6	
					5.0		46.6	
					10.0		65.8	
					0.32	LDT	1.8	
					0.63		4.4	
					1.25		12.0	
					2.5		25.2	
					5.0		37.6	
					10.0		48.2	
Thymol	5-Methyl-2-(propan-2-yl)phenol		Produced synthetically	Essential oil	17.47	EHT	99	Katiki et al. (2017b)
			Lippia origanoides Kunth (=*Lippia sidoides* Cham.)/Verbenaceae	Essential oil	0.31	EHT	9.9	Camurça-Vasconcelos et al. (2007)
					0.62		93.6	
					1.25		98.2	
					1.25	LDT	33.0	
					2.5		54.8	
					5.0		73.9	
					10.0		99.2	
					20.0		99.7	
Citronellal	3,7-Dimethyloct-6-enal		Produced synthetically	Essential oil	5.0	EHT	99	Katiki et al. (2017b)
			Corymbia citriodora (Hook.) K.D. Hill and L.A.S. Johnson (=*Eucalyptus citriodora* Hook.)/Myrtaceae	Essential oil	0.75	AWMT	37.50	Araújo-Filho et al. (2019)
					1		54.16	
					1.25		70.83	
					1.5		83.33	
					1.75		95.83	
					2		100	
Lectin	9-Benzyl-3-methylidene-1,5-bis-(4-methylphenyl)sulfonyl-1,5,9-triazacyclododecane		*Parkia platycephala* Benth/Leguminosae	Protein	1.2	LDT	-	Silva et al. (2019)
					LET	-		
					0.31	LDT	50	

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TABLE 3 | (*Continued*) Plant compounds efficacy against *H. contortus*.

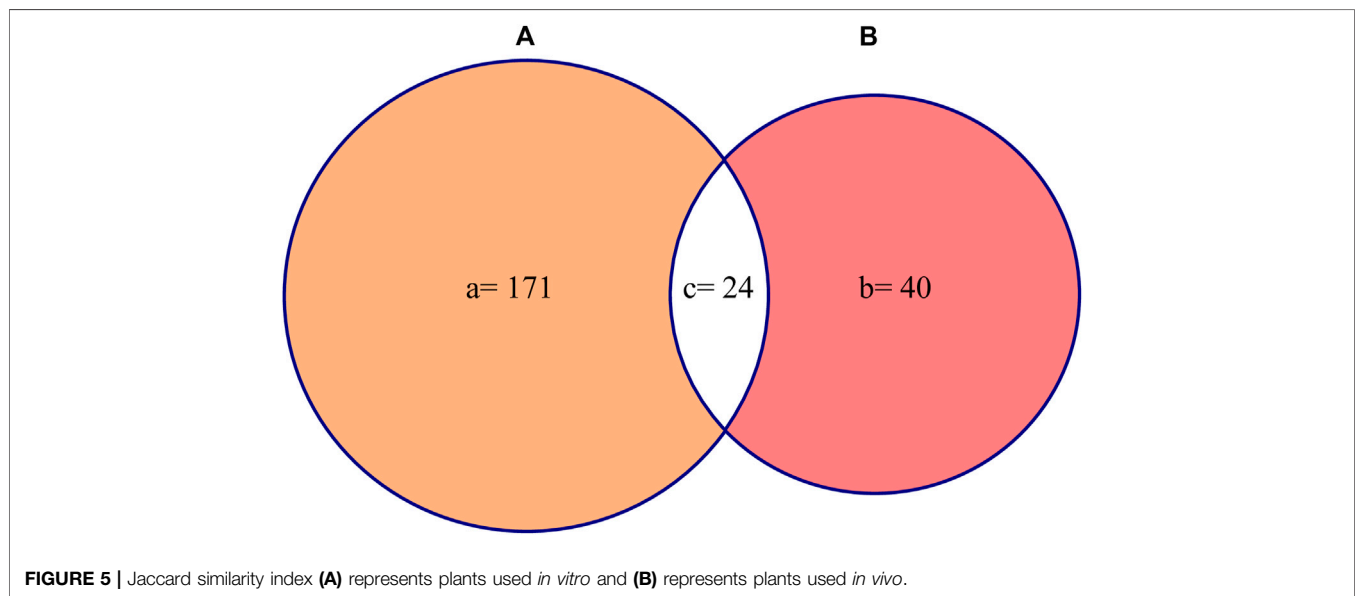| Compound name	IUPAC name	Chemical structure	Plant name/family	Extract	Concentration (mg/ml)	Assays	Inhibition (%)	References
Goniothalamin	(2*R*)-2-[(*E*)-2-phenylethenyl]-2,3-dihydropyran-6-one		*Cryptocarya massoy* (Oken) Kosterm. (=*Cryptocarya novoguineensis* Teschner)/ Lauraceae	NA	200–300 µM 6.25 µM	LDT LMT	IC_{50} IC_{50}	Herath et al. (2019)
Dihydrokavain	(2 S)-4-methoxy-2-(2-phenylethyl)-2,3-dihydropyran-6-one		*Piper methysticum* G. Forst./ Piperaceae	NA	207 µM	LDT LMT	IC_{50} -	Herath et al. (2019)
Desmethoxyyangonin	4-Methoxy-6-[(E)-2-phenylethenyl]pyran-2-one		*P. methysticum* G. Forst./ Piperaceae	NA	31.7 µM	LDT LMT	IC_{50} -	Herath et al. (2019)
Yangonin	4-Methoxy-6-[(E)-2-(4-methoxyphenyl) ethenyl] pyran-2-one		*P. methysticum* G. Forst./ Piperaceae	NA	23.7 µM	LDT LMT	IC_{50} -	Herath et al. (2019)
Carvone*	2-Methyl-5-prop-1-en-2-ylcyclohex-2-en-1-one		Supplied by GRASP Ind. E com. (Curitibia-PR, Brazil)	Encapsulated oil	50	FEC	Fecal egg count was significantly reduced, decreased male and reproductive capacity of female after 45 days in santa ines lambs	Katiki et al. (2019)
					20		The dose did not affect acquisition of parasites after pasture access and as FEC raised and body weight decreased of morada nova lambs	
Cinnamaldehyde	(E)-3-phenylprop-2-enal		Produced synthetically Produced synthetically	Essential oil Essential oil	0.366 0.085	EHT EHT	99 99	Katiki et al. (2017b) Katiki et al. (2017b)

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TABLE 3 | (*Continued*) Plant compounds efficacy against *H. contortus*.

Compound name	IUPAC name	Chemical structure	Plant name/family	Extract	Concentration (mg/ml)	Assays	Inhibition (%)	References
Vanillin	4-Hydroxy-3-methoxybenzaldehyde		Produced synthetically	Essential oil	815.16	EHT	99	Katiki et al. (2017b)
Limonene	1-Methyl-4-prop-1-en-2-ylcyclohexene		Obtained from citrus peel	Essential oil	207.56	EHT	50	Katiki et al. (2017b)

AWMT, Adult Worm Motility Test; LET, Larval Exsheathment Test; LMT, Larval Motility Test.

FIGURE 5 | Jaccard similarity index **(A)** represents plants used *in vitro* and **(B)** represents plants used *in vivo*.

and due to their easy harvesting and less harmful effect on plant life, make them as the first choice of herbalists (Bhat et al., 2013; Tariq et al., 2017).

Medicinal plants owing to their potential of having a significant source of bioactive compounds that may lead to the development of novel drugs (Azwanida, 2015; Ali et al., 2020). Scientists have analyzed and evaluated the effect of various kinds of solvents, for the purpose to extract these bioactive compounds from various plant parts (Altemimi et al., 2017). Extraction is the separation of medicinally active portions of a plant, using selective solvents through standard procedures (Azwanida, 2015). The purpose of extraction is to separate the soluble plant metabolites, leaving behind the insoluble cellular marc (residue) (Azwanida, 2015). Methanol was the most preferred solvent for plant extraction possibly owing to its polar nature that ensures the release of several bioactive compounds from plants. It has been scientifically proven that highly polar solvents should be used to extract different bioactive compounds with high accuracy (Altemimi et al., 2017). Fruitful results of active compound in plants mainly depend upon the solvent used for herbal formulation.
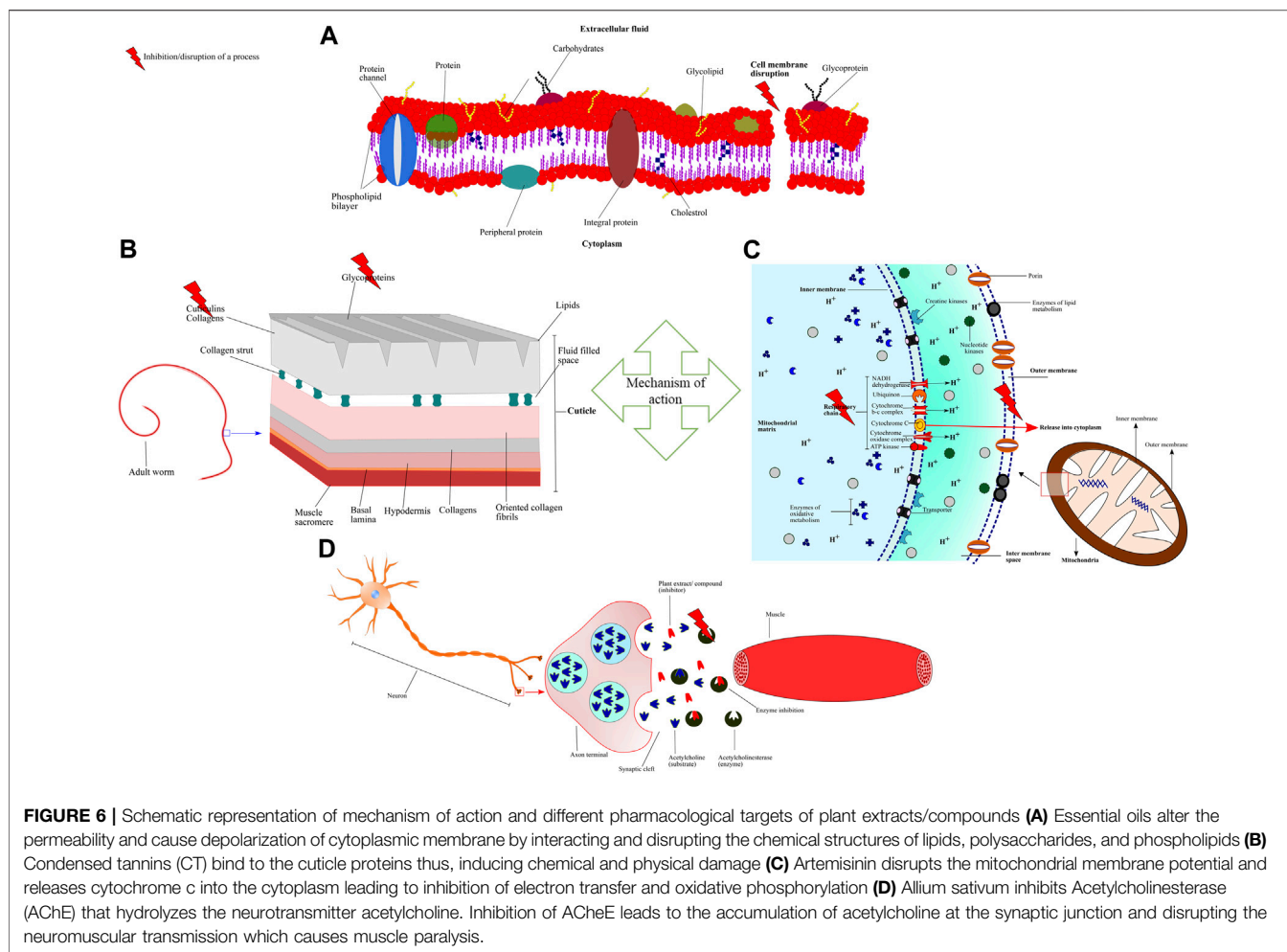
The results revealed that more studies were conducted to evaluate *in vitro* anthelmintic activities of medicinal plants as compared to *in vivo*. *In vitro* validation of medicinal plants provides the proof of reliability of these plants against *H. contortus*. In veterinary parasitology several *in vitro* techniques are broadly used for analysis of nematicidal activity of drugs/plant extracts prior to *in vivo* testing (Sangster and Gill, 1999). There are several positive aspects of *in vitro* assays prior to *in vivo* including less time consuming, less expensive, need for a smaller number of animals, and permitting the evaluation of the efficacy of different anthelmintic compounds throughout the life cycle of the parasite (Demeler et al., 2013). Based on the reliable results obtained from *in vitro* analysis further selection of extract/pure compound for *in vivo* evaluation can be carried-out (Zips et al.,

2005). *In vivo* studies are mainly conducted to evaluate the mechanism of action of the desired extract/compound, the immune response of the host animal, toxicity levels, as well as the *in vivo* effectiveness. Although there are many advantages of *in vivo* studies, but there are also some shortcomings including more time consuming, expensive, and lower precision and reproducibility (Lacey et al., 1990). These limitations should be taken into account and highlight the significance of pharmaceutical/pharmacokinetic studies for the industrial development of new anthelmintic products against *H. contortus*. The research to find effective and natural anthelmintics has been highly inundated with *in vitro* studies, hence, it is suggested to evaluate the plant extracts/compounds *in vivo* in future.

Pharmacological Action

Pharmacological activity of an extract/compounds/drug depends on how the candidate interacts with enzymes, proteins, nucleic acids, biomolecules, and different types of receptors (Roy, 2011). Pharmacological activity is an important phenomenon to know the precise target of the drug/extract/compound with anthelmintic efficacy against the parasite or other organism/ pathogen under observation (**Figure 6**).

A. sativum ethanolic extract inhibits the motility of the *H. contortus* through a destructive and inhibitive effect on the enzyme acetylcholinesterase (AChE). The enzyme rapidly hydrolyzes acetylcholine (neurotransmitter) and thus, limits and terminates the cholinergic synaptic transmission (Taylor, 1990; Lee, 1996). Inhibition of ACheE leads to the accumulation of acetylcholine, thereby interrupting the neuromuscular transmission causes paralysis of musculature. Due to muscular discoordination/paralysis food swallowing and movement through the digestive system is stopped. The parasites enter the state of starvation and energy deprivation and thus, unable to survive inside the host (Kaur and Sood, 1982; Opperman and

FIGURE 6 | Schematic representation of mechanism of action and different pharmacological targets of plant extracts/compounds **(A)** Essential oils alter the permeability and cause depolarization of cytoplasmic membrane by interacting and disrupting the chemical structures of lipids, polysaccharides, and phospholipids **(B)** Condensed tannins (CT) bind to the cuticle proteins thus, inducing chemical and physical damage **(C)** Artemisinin disrupts the mitochondrial membrane potential and releases cytochrome c into the cytoplasm leading to inhibition of electron transfer and oxidative phosphorylation **(D)** Allium sativum inhibits Acetylcholinesterase (AChE) that hydrolyzes the neurotransmitter acetylcholine. Inhibition of ACheE leads to the accumulation of acetylcholine at the synaptic junction and disrupting the neuromuscular transmission which causes muscle paralysis.

Chang, 1992). The antiparasitic activity of *A. sativum* may also be attributed to the sulfur containing compounds (e.g., ajoene and allicin) which can possibly form disulphide bonds with free thiol groups, and thus, inhibit enzymes or other proteins, which are important for survival of the parasite (Krstin et al., 2018). Crude aqueous extract of *Achillea millefolium* L. has profound anthelmintic activity, this could be due to the presence of several key chemical constituents one of which is eugenol. It is reported that eugenol can cause alteration of cell shape, membrane blebs (Machado et al., 2011), restrict cell growth, swelling, and collapsing cell membrane and arrest cell division (Ueda-Nakamura et al., 2006). The compound artemisinin of *A. absinthium* can inhibit vital enzymes of metabolic cascade by forming covalent bonds and resulting in irreversible inhibition of the enzyme (s) activities. The enzymes include S-adenosyl-methionine synthesase (SAMS), spermidine synthase (SpdSyn), L-lactate dehydrogenase (LDH), pyruvate kinase, and ornithine aminotransferase (OAT) (Wang et al., 2015). Artemisinin is also reported to disrupt mitochondrial membrane potential, cause cytochrome c release into the cytoplasm (Jia et al., 2016), and inhibit the electron transfer and oxidative phosphorylation of mitochondria, with final activation of caspase-3-mediated apoptosis (Li et al., 2005). Additionally, crude aqueous extract of *A. absinthium* can induce ultrastructural changes

such as tegumental damage, nephridial canal epithelium lining and intrauterine eggs destruction, lipid accumulation, glycogen depletion, and finally worm paralysis and death (Beshay, 2018). Similar anthelmintic effects of tegumental disorganization/perforation and adult worm paralysis were also observed for *C. procera* aqueous and ethanolic extracts (Khalil et al., 2016). Bromelain extracted from *Ananas comosus* (L.) Merr. stem has been found as potent anthelmintic against gastrointestinal nematodes (Stepek et al., 2004; Domingues et al., 2013). Bromelain removes and digests the cuticle layer of nematodes resulting in immobility and death of the parasites (Stepek et al., 2004; Stepek et al., 2006).

Azadirachta indica A. Juss. leaves contain condensed tannins (CT) (Sakti et al., 2018), which facilitate diffusion of flavonoids by binding to the cuticle proteins (Kerboeuf et al., 2008). Flavonoids and CT inhibit secretion of key enzymes (e.g., esterase, tyrosin kinase, and nonspecific cholinesterase) that may cause fatal intracellular instability, neuromuscular disorganization, energy depletion, paralysis and death of parasites (Hoste et al., 2006; Kerboeuf et al., 2008).

Essential oils of *Corriandrum sativum* L., *C. citratus*, *C. schoenanthus*, *E. staigeriana* and *L. origanoides* were found highly effective against *H. contortus in vitro*. Essential oils may acquire this efficacy owing to a mixture of different chemical constituents whose interaction can result in compounds that

inhibit or disorganize vital functions from the initial stages of development onward, interrupt with parasite metabolic activities, and interfere with drive mechanisms due to possible destructuring of the nervous system (Oka et al., 2000). Furthermore, essential oils can alter the permeability and cause depolarization of cytoplasmic membrane by interacting and disrupting the chemical structures of lipids, polysaccharides, and phospholipids (Bakkali et al., 2008). Phytochemical profile of *Cocos nucifera* L. revealed the presence of alkaloids, flavonoids, phenols, triterpenes, and condensed tannins among others (Lima et al., 2015). The compounds like flavonoids have antioxidant activities, while condensed tannins have shown antiparasitic activities by binding to proteins present in the cuticle, oral cavity, esophagus, and cloaca, thus inducing chemical and physical damage in the parasite (Costa et al., 2010). The efficacy of plant compounds may be attributed to the fact that they inhibit or retard the growth, maturation damage, suppress appetite or reduce procreative ability, which are all the causes of mortality. Moreover, the considerable activity of plants extracts may be due to the additive or synergistic relationship among different major components which can interact with multiple molecular targets in various developmental stages of the parasite to produce a pharmacological effect (Marie-Magdeleine et al., 2009).

H. contortus exposed to *C. citriodora* essential oils demonstrated ultrastructural changes, such as formations of vacuoles, disorganization of muscular layer, and changes in the mitochondrial profile. These changes suggest the loss of homeostasis and loss of motility due to muscular disorganization of the parasite (Araújo-Filho et al., 2019). *E. helioscopia* has monoterpens, which are lipophilic and can penetrate through cell membrane, induce expansion, increase permeability and disturb membrane structure and membrane embedded enzymes (Cox et al., 2000; Samy and Ignacimuthu, 2000; Cox et al., 2001). The nematicidal activity may also be attributed to the presence of tannins, which on the surface of nematodes can form complexes with proteins and result in alteration of metabolic pathways (Min et al., 2004; Ahmed, 2010) and enzymes (cysteine proteinases), which can damage the cuticle and kill the nematode parasites (Stepek et al., 2004; Stepek et al., 2006). Similarly, saponins, amino acids, and sterols can disturb proteins structure (Mabusela et al., 1990) therefore, affecting growth and reparation of nematode body. While compound muzigadial and ajoene has anti-feedant activity and inhibit proliferation of arterial smooth muscle cells and protein prenylation (Ferri et al., 2003; Mohanlall and Odhav, 2009). *L. latisiliquum* leaves forage utilization presented ultrastructural changes; for instance, disturbance of intestinal muscular cells/tissues and cytoplasmic vacuolization, suggesting that different secondary metabolites of leaves may provoke these changes. The alterations to the intestinal cells may be due to the ingestion of active compounds by the parasite, and the resulting direct contact between the bioactive compounds and the intestinal cells. The cytoplasmic vacuolization described can be interpreted as signs of disturbances in cellular functions, possibly due to imbalance of fluid exchanges between the intestinal and pseudocoelomic space and/or between the muscle and the pseudocoelomic space (Martínez-Ortiz-de-Montellano et al., 2019).

The high efficacy of *Nicotiana tabacum* L. against *H. contortus* could be attributed to the presence of nicotine, a ganglion stimulant (Bowman and Rand, 1980). Nematode muscles are known to contain excitatory neuromuscular junctions containing ganglion type nicotinic receptors with acetylcholine as their neurotransmitter (Neal, 2020). Any ganglion stimulant would tend to activate theses neuromuscular junctions causing a spastic paralysis in the worms leading to their death and expulsion from the host (Nouri et al., 2016). Among the reported plants with promising anti-haemonchiasis activity, *L. viridiflorum* leaves are rich in flavonoids and its anthelmintic action of egg hatching inhibition could be due to the effect on enzymatic activity and metabolic processes in helminthes (Kerboeuf et al., 2008).

Different protein contents e.g., proteases, ribosomal proteins, chitinases etc. isolated from *Spigelia anthelmia* L. were effective against different life stages of *H. contortus* (Araujo et al., 2017). Proteases can cause severe damage to the cuticle by disrupting cuticular proteins of the parasite (Liang et al., 2010), in larvae the proteases may hydrolyze/digest the proteins necessary for larval migration (Araujo et al., 2017), and also degrade the egg membrane during egg hatching (Mansfield et al., 1992). Chitinases were also identified which can degrade chitin present in the egg shell (Rogers and Brooks, 1977) and larva, inhibiting their development and leading to death (Rocha et al., 2015).

Comparative analysis also revealed that plant extracts/essential oils were more effective *in vitro* than *in vivo* against various stages of the parasite. Similar differences between *in vitro* and *in vivo* results with plant treatments have been previously reported (Peneluc et al., 2009; Nogueira et al., 2012) and might be related with bioavailability of plant chemical constituents in different parts of the ruminant gastrointestinal tract (Athanasiadou et al., 2007; Eguale et al., 2007b). Furthermore, adult nematodes may also be more resistant to the active components, or rumen microbiota may reduce the activity of metabolites (Nogueira et al., 2012), and other aspects, such as ruminal pH. Mostly, in gerbils the efficacy of plant extracts was reported to be comparatively low than the activity observed in sheep. Using rodents for evaluation of plants anthelmintic activity has some drawbacks, firstly the habitat for nematodes is quite different in rodents and small ruminants, hence, association between habitat and drug site absorption define the higher or lower drug activity (Hennessy, 1997). Secondly, different efficacy obtained in rodents and sheep can be described by mechanism of distribution and biotransformation of the drug in a monogastric and polygastric animal species. However, efficacy test on rodent nematodes can help researchers deduce the prescriptions to be used on sheep and goats (Camurça-Vasconcelos et al., 2007). The studies concerning isolation and purification of plant compounds responsible for antiparasitic acitivities are few and insufficient. Most of the studies reported the presence of key components of the plants which do not provide any information about the effective antiparasitic compounds and their mechanism of action. Therefore, pure comounds isolated from plants should be given focus for *in vitro*, *in vivo* evaluation, toxicology, and pharmacology studies in future research, this will provide baseline information for developing new ecofriendly and cost effective drugs with lesser side effects.

Toxicity Evaluation

Safety issues of herbal medicines have been remained a big question and scientists are being interested in herbal medicines for decades. The notion that "natural" equals "safe" is apparently deceptive, since natural products comprise pharmacologically active compounds which, when taken in high doses or in specific conditions, can be detrimental to health. Bromelain of *A. comosus* is non-toxic and considered safe without any adverse effects and has shown good absorption and therapeutic benefits (Maurer, 2001). Moreover, no alteration in body weight, food, and water consumption was observed. The enzymes, urea, and creatinine levels of serum were also unaltered and no significant difference was observed (Dutta and Bhattacharyya, 2013). *A. millefolium* aqueous extract oral and intraperitoneal administration produced no significant biochemical and histopathological changes in Wistar rats (Cavalcanti et al., 2006). No relevant signs of toxicity were observed for longer periods of exposure, however, slight changes in blood glucose and cholesterol levels, and liver weight were detected, neither correlated with dose or period of exposure nor suggestive of toxicity (Cavalcanti et al., 2006). *C. sativum* was safe and no effects on hematological profile, histology, relative organ weights, and plasma markers of damage vital organs were found. However, a significant body weight loss was observed due to reduction in food intake (Patel et al., 2012), which is suggestive of the disturbances in carbohydrates, proteins, and fats (Ecobichon and Klaassen, 2001). *C. citratus* was safe and produced no toxic effects when tested against mice peritoneal macrophages (Santoro et al., 2007). Similarly, *C. schoenanthus* depicted no toxicological effects on hepatic and renal parameters in lambs (Katiki et al., 2012).

The ethyl acetate extract of *C. nucifera* presented no acute oral toxicity at the tested doses. However, the intraperitoneal and intramuscular administration was toxic (Tayler et al., 2020). Moreover, the hemoglobin level fallen below the normal limit after 8 days, suggesting that the extract could have negative effects if used for longer periods of time (Tayler et al., 2020). Similarly, *E. staigeriana* essential oil when administered orally was non-toxic, while intraperitoneal administration did not depict similar results (Macedo et al., 2010). Traditionally, when a substance administered orally and show LD_{50} value equal to 1000 mg/kg is considered to be safe or less toxic (Garner et al., 1961). The observed difference in toxicity may be attributed to the fact that after oral administration, the extract may be poorly absorbed, detoxified by the liver (Hayes and Loomis, 1996) or degraded by the stomach and gut digestive enzymes, however, during intraperitoneal administration the absorption is systematic and toxicity is stronger and appear earlier (Hayes and Loomis, 1996; Obici et al., 2008).

E. helioscopia was safe and produced no physiological alternations of vital organs and the biochemical parameters were also unchanged at the tested doses (Saleem et al., 2016). *S. anthelmia* and *N. tabacum* did not affect the body weight and animal behavior and were considered to be non-toxic (Ribeiro et al., 2017; Andjani et al., 2019).

Low toxicity of *A. sativum* and *L. viridiflorum* was observed on human HaCat and mammalian macrophages cells, respectively, (Krstin et al., 2018; de Melo et al., 2020). Mice became dead after oral administration of *C. citriodora* essential oil and citronellal suggesting toxicity of the plant species (Araújo-Filho et al., 2019).

Prolonged use of *A. absinthium* and *A. herba-alba* lead to neurotoxicity and infertility by affecting the reproductive system, respectively (Almasad et al., 2007; Lachenmeier, 2010). *A. indica* poisoning affect was dose and time dependent and histopathological analysis showed that the testicles, liver, and kidneys were the organs affected (Deng et al., 2013). *C. procera* latex was found to be toxic at the tested doses, animals developed signs of nervousness, salivation, urination, dyspnea, tachycardia, and loss of condition. Severe pathological changes in intestines, heart, liver, kidneys, lungs, and brain were also observed (Mahmoud et al., 1979). A slight change (decrease) in the serum biochemical profile was also observed. This decrease in serum zinc, iron, and copper concentration (Al-Qarawi et al., 2001) might be due to continue (i) interference of adult parasites in the abomasum with digestibility and absorption of nutritive substances as a results of existing damage to the abomasal mucosa and its digestive function, or (ii) effects of unknown toxic principles elaborated by the worm.

CONCLUSION AND FUTURE RECOMMENDATIONS

Mostly, *in vitro* studies have been performed to evaluate the anti-haemonchiasis activity of plants. *In vitro* studies have a key role in initial screening however, these studies provide no information of bioavailability, toxicity, and *in vivo* efficacy of tested extract/compound. Hence, in future *in vivo* studies by using suitable animal models should be carried out to understand the pharmacokinetics and pharmacodynamics of the tested extract/compound. Most of the *in vivo* studies provide no evidence about toxicity and mechanism of action of the medicinal plant/compound, this is the most neglected aspect and strongly suggested to researchers to evaluate toxicity levels and pharmacological action of the tested plant/compound. *Mentha x vilosa* Huds., *Anthemis nobilis* L (syn. *Chamaemelum nobilis* (L.) All.), *Lantana camara* L., *Trichilia claussenii* C. DC., *Croton macrostachyus* Hochst ex Delile, *Lavandula officinalis* (Chaix and Kitt.), *Coleus maculosus* subsp. edulis (Vatke) A.J.Paton (*Plectranthus punctatus* (L.f) L'Her.), *Maesa lanceolata* Forssk., and *Foeniculum vulgare* Mill. among others were highly effective *in vitro* against different life stages of the parasite, however, these plant species are not tested for *in vivo* efficacy. These plants should be evaluated for *in vivo* anti-haemonchiasis activity along with phytochemical profile, toxicological effects, and pharmacological activity. Most of the reported studies provide no information regarding time exposure and LC_{50} values of medicinal plant/compound used for *in vitro* evaluation. Time exposure and LC_{50} are very important parameters to understand the accurate efficacy of medicinal plants, therefore, it is recommended to provide this information in future studies. Plants contain a number of different compounds, which act synergistically to perform an activity, only few compounds have been isolated and tested *in vitro*/*in vivo* against *H. contortus*. It is recommended to identify/isolate individual compounds and evaluate their activity, this will provide more precise and in depth information of anti-haemonchiasis potential of the medicinal plant under observation. Plant compounds cinnamaldehyde, thymol, and carvacrol have revealed high efficacy in *in vitro* studies, it is recommended to

further investigate these compounds for *in vivo* activity. Carvone and anethole have shown promising anti-haemonchiasis potential *in vitro* and *in vivo*, however, their toxicity levels and pharmacological effects are unknown and should be investigated in future studies. *L. viridiflorum* has revealed high efficacy both *in vitro* and *in vivo* and has no adverse/toxic effects after oral administration and considered to be safe, it is recommended to pharmaceutical industries to further investigate this plant species because it could be an alternative candidate for drug development against *H. contortus*.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.644027/full#supplementary-material.

REFERENCES

Acharya, J., Hildreth, M. B., and Reese, R. N. (2014). *In vitro* screening of forty medicinal plant extracts from the United States Northern Great Plains for anthelmintic activity against *Haemonchus contortus*. *Vet. Parasitol.* 201 (1-2), 75–81. doi:10.1016/j.vetpar.2014.01.008

Ademola, I. O., and Eloff, J. N. (2011). Ovicidal and larvicidal activity of *Cassia alata* leaf acetone extract and fractions on *Haemonchus contortus*: in vitro studies. *Pharm. Biol.* 49 (5), 539–544. doi:10.3109/13880209.2010.526948

Ademola, I. O., Fagbemi, B. O., and Idowu, S. O. (2007). Anthelmintic activity of *Spigelia anthelmia* extract against gastrointestinal nematodes of sheep. *Parasitol. Res.* 101 (1), 63–69. doi:10.1007/s00436-006-0444-0

Ademola, I. O., Fagbemi, B. O., and Idowu, S. O. (2004). Evaluation of the anthelmintic activity of *Khaya senegalensis* extract against gastrointestinal nematodes of sheep: *in vitro* and *in vivo* studies. *Vet. Parasitol.* 122 (2), 151–164. doi:10.1016/j.vetpar.2004.04.001

Ademola, I. O., and Idowu, S. O. (2006). Anthelmintic activity of Leucaena leucocephala seed extract on *Haemonchus contortus* -infective larvae. *Vet. Rec.* 158 (14), 485. doi:10.1136/vr.158.14.485

Ahmad, H., Khan, S. M., Ghafoor, S., and Ali1, N. (2009). Ethnobotanical study of upper Siran. *J. Herbs, Spices Med. Plants* 15 (1), 86–97.

Ahmed, A. H., Ejo, M., Feyera, T., Regassa, D., Mummed, B., and Huluka, S. A. (2020). *In Vitro* anthelmintic activity of crude extracts of *Artemisia herba-alba* and *Punica granatum* against *Haemonchus contortus*. *J. Parasitol. Res.* 2020, 1. doi:10.1155/2020/4950196

Ahmed, M. A. A. (2010). *Gastrointestinal (nematode) infections in small ruminants: epidemiology, anthelmintic efficacy and the effect of wattle tannins.*

Ahmed, M., Laing, M. D., and Nsahlai, I. V. (2013). *In vitro* anthelmintic activity of crude extracts of selected medicinal plants against *Haemonchus contortus* from sheep. *J. Helminthol.* 87 (2), 174–179. doi:10.1017/s0022149x1200020x

Aiyegoro, O., and Okoh, A. (2009). Use of bioactive plant products in combination with standard antibiotics: implications in antimicrobial chemotherapy. *J. Med. Plants Res.* 3 (13), 1147–1152.

Ali, R., Khan, S., Khan, M., Adnan, M., Ali, I., and Khan, T. A., et al. (2020). A systematic review of medicinal plants used against Echinococcus granulosus. *PLoS One* 15 (10), e0240456. doi:10.1371/journal.pone.0240456

Al-Qarawi, A. A., Mahmoud, O., Sobaih, M., Haroun, E., and Adam, S. (2001). A preliminary study on the anthelmintic activity of *Calotropis procera* latex against *Haemonchus contortus* infection in Najdi sheep. *Vet. Res. Commun.* 25 (1), 61–70. doi:10.1023/a:1026762002947

Al-Shaibani, I., Phulan, M., Arijo, A., and Qureshi, T. (2008). Ovicidal and larvicidal properties of *Adhatoda vasica* (L.) extracts against gastrointestinal nematodes of sheep *in vitro*. *Pak Vet. J.* 28 (2), 79–83.

Almasad, M. M., Qazan, W. S., and Daradka, H. (2007). Reproductive toxic effects of *Artemisia herba alba* ingestion in female Spague-Dawley rats. *Pak J. Biol. Sci.* 10 (18), 3158–3161. doi:10.3923/pjbs.2007.3158.3161

Alowanou, G. G., Olounladé, P. A., Akouèdegni, G. C., Faihun, A. M. L., Koudandé, D. O., and Hounzangbé-Adoté, S. (2019). *In vitro* anthelmintic effects of *Bridelia ferruginea, Combretum glutinosum*, and *Mitragyna inermis* leaf extracts on *Haemonchus contortu*s, an abomasal nematode of small ruminants. *Parasitol. Res.* 118 (4), 1215–1223. doi:10.1007/s00436-019-06262-5

Altemimi, A., Lakhssassi, N., Baharlouei, A., Watson, D., and Lightfoot, D. (2017). Phytochemicals: extraction, isolation, and identification of bioactive compounds from plant extracts. *Plants* 6 (4), 42. doi:10.3390/plants6040042

Andjani, H., Sentosa, Y., Yati, K., Fauzantoro, A., Gozan, M., and Yoo, Y. (2019). Acute oral toxicity test of nicotiana tabacum L. Bio-oil against female winstar rats. Paper presented at the IOP Conference Series: Earth and Environmental Science.

André, W. P. P., Paiva Junior, J. R. d., Cavalcante, G. S., Ribeiro, W. L. C., Araújo Filho, J. V. d., Santos, J. M. L. d., et al. (2020). Anthelmintic activity of nanoencapsulated carvacryl acetate against gastrointestinal nematodes of sheep and its toxicity in rodents. *Rev. Bras. Parasitol. Vet.* 29 (1), e013119. doi:10.1590/s1984-29612019098

Andre, W. P. P., Ribeiro, W. L. C., Cavalcante, G. S., Santos, J. M. L. d., Macedo, I. T. F., Paula, H. C. B. d., et al. (2016). Comparative efficacy and toxic effects of carvacryl acetate and carvacrol on sheep gastrointestinal nematodes and mice. *Vet. Parasitol.* 218, 52–58. doi:10.1016/j.vetpar.2016.01.001

Araujo, S. A., Soares, A. M. d. S., Silva, C. R., Almeida Júnior, E. B., Rocha, C. Q., Ferreira, A. T. d. S., et al. (2017). *In vitro* anthelmintic effects of *Spigelia anthelmia* protein fractions against *Haemonchus contortus*. *PLoS One* 12 (12), e0189803. doi:10.1371/journal.pone.0189803

Araújo-Filho, J. V. d., Ribeiro, W. L. C., André, W. P. P., Cavalcante, G. S., Rios, T. T., Schwinden, G. M., et al. (2019). Anthelmintic activity of *Eucalyptus citriodora* essential oil and its major component, citronellal, on sheep gastrointestinal nematodes. *Rev. Bras. Parasitol. Vet.* 28 (4), 644–651. doi:10.1590/s1984-29612019090

Assis, L., Bevilaqua, C., Morais, S., Vieira, L., Costa, C., and Souza, J. (2003). Ovicidal and larvicidal activity *in vitro* of *Spigelia anthelmia* Linn. extracts on *Haemonchus contortus*. *Vet. Parasitol.* 117 (1-2), 43–49. doi:10.1016/j.vetpar.2003.07.021

Athanasiadou, S., Githiori, J., and Kyriazakis, I. (2007). Medicinal plants for helminth parasite control: facts and fiction. *Animal* 1 (9), 1392–1400. doi:10.1017/s1751731107000730

Athanasiadou, S., Kyriazakis, I., Jackson, F., and Coop, R. L. (2001). Direct anthelmintic effects of condensed tannins towards different gastrointestinal nematodes of sheep: *in vitro* and *in vivo* studies. *Vet. Parasitol.* 99 (3), 205–219. doi:10.1016/s0304-4017(01)00467-8

Azwanida, N. (2015). A review on the extraction methods use in medicinal plants, principle, strength and limitation. *Med. Aromat Plants* 4 (196), 2167. doi:10.4172/2167-0412.1000196

Bakkali, F., Averbeck, S., Averbeck, D., and Idaomar, M. (2008). Biological effects of essential oils - a review. *Food Chem. Toxicol.* 46 (2), 446–475. doi:10.1016/j.fct.2007.09.106

Barone, C. D., Zajac, A. M., Manzi-Smith, L. A., Howell, A. B., Reed, J. D., Krueger, C. G., et al. (2018). Anthelmintic efficacy of cranberry vine extracts on ovine *Haemonchus contortus*. *Vet. Parasitol.* 253, 122–129. doi:10.1016/j.vetpar.2018.02.016

Beshay, E. V. N. (2018). Therapeutic efficacy of *Artemisia absinthium* against *Hymenolepis nana*: *in vitro* and *in vivo* studies in comparison with the anthelmintic praziquantel. *J. Helminthol.* 92 (3), 298–308. doi:10.1017/s0022149x17000529

Bhat, J. A., Kumar, M., and Bussmann, R. W. (2013). Ecological status and traditional knowledge of medicinal plants in kedarnath wildlife sanctuary of garhwal himalaya, India. *J. Ethnobiol. Ethnomedicine* 9 (1), 1. doi:10.1186/1746-4269-9-1

Bowman, W. C., and Rand, M. J. (1980). *Textbook of pharmacology*. Blackwell Scientific Publications.

Bruneton, J. (1993). Pharmacognosie: phytochimie plantes médicinales.

Bucar, F., Wube, A., and Schmid, M. (2013). Natural product isolation - how to get from biological material to pure compounds. *Nat. Prod. Rep.* 30 (4), 525–545. doi:10.1039/c3np20106f

Cabardo, D. E., Jr, and Portugaliza, H. P. (2017). Anthelmintic activity of *Moringa oleifera* seed aqueous and ethanolic extracts against *Haemonchus contortus* eggs and third stage larvae. *Int. J. Vet. Sci. Med.* 5 (1), 30–34. doi:10.1016/j.ijvsm.2017.02.001

Cala, A. C., Chagas, A. C. S., Oliveira, M. C. S., Matos, A. P., Borges, L. M. F., Sousa, L. A. D., et al. (2012). *In vitro* anthelmintic effect of *Melia azedarach* L. and *Trichilia claussenii* C. against sheep gastrointestinal nematodes. *Exp. Parasitol.* 130 (2), 98–102. doi:10.1016/j.exppara.2011.12.011

Camurça-Vasconcelos, A., Bevilaqua, C., Morais, S., Maciel, M., Costa, C., Macedo, I., et al. (2007). Anthelmintic activity of *Croton zehntneri* and *Lippia sidoides* essential oils. *Vet. Parasitol.* 148 (3-4), 288–294. doi:10.1016/j.vetpar.2007.06.012

Carvalho, C. C. d., Machado, K. N., Ferreira, P. M. P., Pessoa, C., Fonseca, T. H. S., Gomes, M. A., et al. (2013). Biological screening of extracts of Brazilian Asteraceae plants.

Carvalho, C. O., Chagas, A. C. S., Cotinguiba, F., Furlan, M., Brito, L. G., Chaves, F. C., et al. (2012). The anthelmintic effect of plant extracts on *Haemonchus contortus* and *Strongyloides venezuelensis*. *Vet. Parasitol.* 183 (3-4), 260–268. doi:10.1016/j.vetpar.2011.07.051

Castillo-Mitre, G. F., Olmedo-Juárez, A., Rojo-Rubio, R., González-Cortázar, M., Mendoza-de Gives, P., Hernández-Beteta, E. E., et al. (2017). Caffeoyl and coumaroyl derivatives from *Acacia cochliacantha* exhibit ovicidal activity against *Haemonchus contortus*. *J. Ethnopharmacology* 204, 125–131. doi:10.1016/j.jep.2017.04.010

Cavalcante, G. S., de Morais, S. M., Andre, W. P. P., Ribeiro, W. L. C., Rodrigues, A. L. M., De Lira, F. C. M. L., et al. (2016). Chemical composition and *in vitro* activity of *Calotropis procera* (Ait.) latex on *Haemonchus contortus*. *Vet. Parasitol.* 226, 22–25. doi:10.1016/j.vetpar.2016.06.012

Cavalcanti, A. M., Baggio, C. H., Freitas, C. S., Rieck, L., de Sousa, R. S., Da Silva-Santos, J. E., et al. (2006). Safety and antiulcer efficacy studies of *Achillea millefolium* L. after chronic treatment in Wistar rats. *J. Ethnopharmacology* 107 (2), 277–284. doi:10.1016/j.jep.2006.03.011

Cortes-Morales, J. A., Olmedo-Juárez, A., Trejo-Tapia, G., González-Cortazar, M., Domínguez-Mendoza, B. E., Mendoza-de Gives, P., et al. (2019). *In vitro* ovicidal activity of *Baccharis conferta* Kunth against *Haemonchus contortus*. *Exp. Parasitol.* 197, 20–28. doi:10.1016/j.exppara.2019.01.003

Costa, C., Bevilaqua, C., Camurça-Vasconcelos, A., Maciel, M., Morais, S., Castro, C., et al. (2008). *In vitro* ovicidal and larvicidal activity of *Azadirachta indica* extracts on *Haemonchus contortus*. *Small Rumin Res.* 74 (1-3), 284–287. doi:10.1016/j.smallrumres.2007.09.003

Costa, C. T. C., Bevilaqua, C. M. L., Morais, S. M., Camurça-Vasconcelos, A. L. F., Maciel, M. V., Braga, R. R., et al. (2010). Anthelmintic activity of *Cocos nucifera* L. on intestinal nematodes of mice. *Res. Vet. Sci.* 88 (1), 101–103. doi:10.1016/j.rvsc.2009.05.008

Cox, S. D., Mann, C. M., Markham, J. L., Bell, H. C., Gustafson, J. E., Warmington, J. R., et al. (2000). The mode of antimicrobial action of the essential oil of *Melaleuca alternifolia* (tea tree oil). *J. Appl. Microbiol.* 88 (1), 170–175. doi:10.1046/j.1365-2672.2000.00943.x

Cox, S., Mann, C., Markham, J., Gustafson, J., Warmington, J., and Wyllie, S. (2001). Determining the antimicrobial actions of tea tree oil. *Molecules* 6 (2), 87–91. doi:10.3390/60100087

de Araújo-Filho, J. V., Ribeiro, W. L. C., André, W. P. P., Cavalcante, G. S., Guerra, M. d. C. M., Muniz, C. R., et al. (2018). Effects of *Eucalyptus citriodora* essential oil and its major component, citronellal, on *Haemonchus contortus* isolates susceptible and resistant to synthetic anthelmintics. *Ind. Crops Prod.* 124, 294–299. doi:10.1016/j.indcrop.2018.07.059

De Jesús-Gabino, A. F., Mendoza-de Gives, P., Salinas-Sánchez, D. O., López-Arellano, M. E., Liébano-Hernández, E., Hernández-Velázquez, V. M., et al. (2010). Anthelmintic effects of *Prosopis laevigata*-hexanic extract against *Haemonchus contortus* in artificially infected gerbils (*Meriones unguiculatus*). *J. Helminthol.* 84 (1), 71–75. doi:10.1017/s0022149x09990332

de Melo, A. R. B., Maciel Higino, T. M., da Rocha Oliveira, A. D. P., Fontes, A., da Silva, D. C. N., de Castro, M. C. A. B., et al. (2020). *Lippia sidoides* and *Lippia origanoides* essential oils affect the viability, motility and ultrastructure of *Trypanosoma cruzi*. *Micron* 129, 102781. doi:10.1016/j.micron.2019.102781

de Oliveira, L. M. B., Bevilaqua, C. M. L., Macedo, I. T. F., de Morais, S. M., Machado, L. K. A., Campello, C. C., et al. (2011). Effects of *Myracrodruon urundeuva* extracts on egg hatching and larval exsheathment of *Haemonchus contortus*. *Parasitol. Res.* 109 (3), 893. doi:10.1007/s00436-011-2331-6

Demeler, J., Gill, J. H., von Samson-Himmelstjerna, G., and Sangster, N. C. (2013). The *in vitro* assay profile of macrocyclic lactone resistance in three species of sheep trichostrongyloids. *Int. J. Parasitol. Drugs Drug Resist.* 3, 109–118. doi:10.1016/j.ijpddr.2013.04.002

Deng, Y.-x., Cao, M., Shi, D.-x., Yin, Z.-q., Jia, R.-y., Xu, J., et al. (2013). Toxicological evaluation of neem (*Azadirachta indica*) oil: acute and subacute toxicity. *Environ. Toxicol. Pharmacol.* 35 (2), 240–246. doi:10.1016/j.etap.2012.12.015

Dixit, A. K., Das, G., Dixit, P., and Sharma, R. L. (2019). Efficacy of herbal extracts and closantel against fenbendazole-resistant *Haemonchus contortus*. *J. Helminthol.* 93 (5), 529–532. doi:10.1017/s0022149x18000627

Domingues, L. F., Giglioti, R., Feitosa, K. A., Fantatto, R. R., Rabelo, M. D., de Sena Oliveira, M. C., et al. (2013). *In vitro* and *in vivo* evaluation of the activity of pineapple (*Ananas comosus*) on *Haemonchus contortus* in Santa Inês sheep. *Vet. Parasitol.* 197 (1-2), 263–270. doi:10.1016/j.vetpar.2013.04.031

Dutta, S., and Bhattacharyya, D. (2013). Enzymatic, antimicrobial and toxicity studies of the aqueous extract of *Ananas comosus* (pineapple) crown leaf. *J. Ethnopharmacology* 150 (2), 451–457. doi:10.1016/j.jep.2013.08.024

Ecobichon, D. J., and Klaassen, C. (2001). *Casarett and Doull's Toxicology: the basic science of poisons* Toxic effects of pesticides. New York: McGraw-Hill, 769–774.

Eguale, T., Tadesse, D., and Giday, M. (2011). *In vitro* anthelmintic activity of crude extracts of five medicinal plants against egg-hatching and larval development of *Haemonchus contortus*. *J. Ethnopharmacology* 137 (1), 108–113. doi:10.1016/j.jep.2011.04.063

Eguale, T., Tilahun, G., Debella, A., Feleke, A., and Makonnen, E. (2007a). *Haemonchus contortus*: *in vitro* and *in vivo* anthelmintic activity of aqueous and hydro-alcoholic extracts of *Hedera helix*. *Exp. Parasitol.* 116 (4), 340–345. doi:10.1016/j.exppara.2007.01.019

Eguale, T., Tilahun, G., Debella, A., Feleke, A., and Makonnen, E. (2007b). *In vitro* and *in vivo* anthelmintic activity of crude extracts of *Coriandrum sativum* against *Haemonchus contortus*. *J. Ethnopharmacology* 110 (3), 428–433. doi:10.1016/j.jep.2006.10.003

Féboli, A., Laurentiz, A. C., Soares, S. C. S., Augusto, J. G., Anjos, L. A., Magalhães, L. G., et al. (2016). Ovicidal and larvicidal activity of extracts of *Opuntia ficus-indica* against gastrointestinal nematodes of naturally infected sheep. *Vet. Parasitol.* 226, 65–68. doi:10.1016/j.vetpar.2016.06.030

Ferreira, L. E., Benincasa, B. I., Fachin, A. L., Contini, S. H. T., França, S. C., Chagas, A. C. S., et al. (2018). Essential oils of *Citrus aurantifolia*, *Anthemis nobile* and *Lavandula officinalis*: *in vitro* anthelmintic activities against *Haemonchus contortus*. *Parasite. Vector* 11 (1), 269. doi:10.1186/s13071-018-2849-x

Ferreira, L. E., Benincasa, B. I., Fachin, A. L., França, S. C., Contini, S. S. H. T., Chagas, A. C. S., et al. (2016). *Thymus vulgaris* L. essential oil and its main

component thymol: anthelmintic effects against *Haemonchus contortus* from sheep. *Vet. Parasitol.* 228, 70–76. doi:10.1016/j.vetpar.2016.08.011

Ferreira, L. E., Castro, P. M. N., Chagas, A. C. S., França, S. C., and Beleboni, R. O. (2013). *In vitro* anthelmintic activity of aqueous leaf extract of Annona muricata L. (Annonaceae) against *Haemonchus contortus* from sheep. *Exp. Parasitol.* 134 (3), 327–332. doi:10.1016/j.exppara.2013.03.032

Ferri, N., Yokoyama, K., Sadilek, M., Paoletti, R., Apitz-Castro, R., Gelb, M. H., et al. (2003). Ajoene, a garlic compound, inhibits protein prenylation and arterial smooth muscle cell proliferation. *Br. J. Pharmacol.* 138 (5), 811–818. doi:10.1038/sj.bjp.0705126

Fouche, G., Sakong, B. M., Adenubi, O. T., Pauw, E., Leboho, T., Wellington, K. W., et al. (2016). Anthelmintic activity of acetone extracts from South African plants used on egg hatching of *Haemonchus contortus*. *Onderstepoort J. Vet. Res.* 83 (1), 1–7. doi:10.4102/ojvr.v83i1.1164

Gaínza, Y. A., Domingues, L. F., Perez, O. P., Rabelo, M. D., López, E. R., and Chagas, A. C. d. S. (2015). Anthelmintic activity *in vitro* of Citrus sinensis and Melaleuca quinquenervia essential oil from Cuba on *Haemonchus contortus*. *Ind. Crops Prod.* 76, 647–652. doi:10.1016/j.indcrop.2015.07.056

Garner, R. J., Clarke, E. G. C., and Clarke, M. L. (1961). *Veterinary toxicology: baillière*. Tindall and Cox London. doi:10.1002/jps.3030470329

Getachew, S., Ibrahim, N., Abebe, B., and Eguale, T. (2012). *In vitro* evaluation of Anthelmintic activities of crude extracts of selected medicinal plants against *Haemonchus contortus* in AlemgenaWereda, Ethiopia. *APG* 3, 20–27. doi:10.5829/idosi.apg.2012.3.2.64177

Gilleard, J. S. (2006). Understanding anthelmintic resistance: the need for genomics and genetics. *Int. J. Parasitol.* 36 (12), 1227–1239. doi:10.1016/j.ijpara.2006.06.010

Githiori, J. B., Höglund, J., Waller, P. J., and Baker, R. L. (2004). Evaluation of anthelmintic properties of some plants used as livestock dewormers against *Haemonchus contortus* infections in sheep. *Parasitology* 129 (2), 245–253. doi:10.1017/s0031182004005566

Hajaji, S., Alimi, D., Jabri, M. A., Abuseir, S., Gharbi, M., and Akkari, H. (2018). Anthelmintic activity of Tunisian chamomile (Matricaria recutita L.) against *Haemonchus contortus*. *J. Helminthol.* 92 (2), 168–177. doi:10.1017/s0022149x17000396

Hamad, K. K., Iqbal, Z., Abbas, R. Z., Khan, A., Muhammad, G., and Epperson, B. (2014). Combination of Nicotiana tabacum and Azadirachta indica: a novel substitute to control levamisole and ivermectin-resistant *Haemonchus contortus* in ovine. *Pak Vet. J.* 8318(1):2074–7764.

Hassan, M., Ra, M., Joshi, T., Yatoo, F. A., and Habib, H. (2019). *In vitro* anthelmintic activity of Abutilon theophrasti Medik.(malvaceae) against eggs and l3 larvae of *Haemonchus contortus*. *Vitro Mol Toxicol* Asian Journal of Pharmaceutical and Clinical Research(3).

Hayes, A. W., and Loomis, T. A. (1996). *Loomis's essentials of toxicology*. Elsevier.

Heckendorn, F., Häring, D. A., Maurer, V., Zinsstag, J., Langhans, W., and Hertzberg, H. (2006). Effect of sainfoin (Onobrychis viciifolia) silage and hay on established populations of *Haemonchus contortus* and Cooperia curticei in lambs. *Vet. Parasitol.* 142 (3-4), 293–300. doi:10.1016/j.vetpar.2006.07.014

Hennessy, D. (1997). Modifying the formulation or delivery mechanism to increase the activity of anthelmintic compounds. *Vet. Parasitol.* 72 (3-4), 367–390. doi:10.1016/s0304-4017(97)00106-4

Herath, H. M. P. D., Preston, S., Jabbar, A., Garcia-Bustos, J., Addison, R. S., Hayes, S., et al. (2019). Selected α-pyrones from the plants Cryptocarya novoguineensis (Lauraceae) and Piper methysticum (Piperaceae) with activity against *Haemonchus contortus in vitro*. *Int. J. Parasitol. Drugs Drug Resist.* 9, 72–79. doi:10.1016/j.ijpddr.2018.12.006

Hernández-Villegas, M., Borges-Argáez, R., Rodriguez-Vivas, R., Torres-Acosta, J., Méndez-González, M., and Caceres-Farfan, M. (2011). Ovicidal and larvicidal activity of the crude extracts from Phytolacca icosandra against *Haemonchus contortus*. *Vet. Parasitol.* 179 (1-3), 100–106. doi:10.1016/j.vetpar.2011.02.019

Hördegen, P., Cabaret, J., Hertzberg, H., Langhans, W., and Maurer, V. (2006). *In vitro* screening of six anthelmintic plant products against larval *Haemonchus contortus* with a modified methyl-thiazolyl-tetrazolium reduction assay. *J. Ethnopharmacology* 108 (1), 85–89. doi:10.1016/j.jep.2006.04.013

Hoste, H., Jackson, F., Athanasiadou, S., Thamsborg, S. M., and Hoskin, S. O. (2006). The effects of tannin-rich plants on parasitic nematodes in ruminants. *Trends Parasitol.* 22 (6), 253–261. doi:10.1016/j.pt.2006.04.004

Hounzangbe-Adote, M. S., Paolini, V., Fouraste, I., Moutairou, K., and Hoste, H. (2005). *In vitro* effects of four tropical plants on three life-cycle stages of the parasitic nematode, *Haemonchus contortus*. *Res. Vet. Sci.* 78 (2), 155–160. doi:10.1016/j.rvsc.2004.05.009

Hussien, J., Urgessa, K., Regassa, F., Jemal, A., Abajebel, S., and Hussien, N. (2011). Antihelmentic effects of the essential oil extracts of selected medicinal plants against *Haemonchus contortus*. *Int. J. Agric. Res.* 6 (3), 290–298. doi:10.3923/ijar.2011.290.298

Idris, U. E., Adam, S. E., and Tartour, G. (1982). The anthelmintic efficacy of Artemisia herba-alba against *Haemonchus contortus* infection in goats. *Natl. Inst. Anim. Health Q. (Tokyo)* 22 (3), 138–143.

Iqbal, Z., Lateef, M., Ashraf, M., and Jabbar, A. (2004). Anthelmintic activity of Artemisia brevifolia in sheep. *J. Ethnopharmacol* 93 (2-3), 265–268. doi:10.1016/j.jep.2004.03.046

Iqbal, Z., Lateef, M., Jabbar, A., Akhtar, M. S., and Khan, M. N. (2006a). Anthelmintic activity ofVernonia anthelmintica. Seeds against trichostrongylid nematodes of sheep. *Pharm. Biol.* 44 (8), 563–567. doi:10.1080/13880200600896512

Iqbal, Z., Lateef, M., Jabbar, A., Ghayur, M. N., and Gilani, A. H. (2006b). *In vitro* andIn vivo anthelmintic activity ofNicotiana tabacum L. leaves against gastrointestinal nematodes of sheep. *Phytother. Res.* 20 (1), 46–48. doi:10.1002/ptr.1800

Iqbal, Z., Lateef, M., Jabbar, A., Muhammad, G., and Khan, M. N. (2005). Anthelmintic activity of Calotropis procera (Ait.) Ait. F. flowers in sheep. *J. Ethnopharmacology* 102 (2), 256–261. doi:10.1016/j.jep.2005.06.022

Iqbal, Z., Lateef, M., Khan, M. N., Jabbar, A., and Akhtar, M. S. (2006c). Anthelmintic activity of Swertia chirata against gastrointestinal nematodes of sheep. *Fitoterapia* 77 (6), 463–465. doi:10.1016/j.fitote.2006.05.010

Iqbal, Z., Munir, M. A., Khan, M., Akhtar, M. S., Javed, I., and Of, O. (2001a). *In vitro* inhibitory effects of Sorghum bicolor on hatching and moulting of *Haemonchus contortus* eggs. *Prospects* 3, 451–453.

Iqbal, Z., Nadeem, Q. K., Khan, M., Akhtar, M., and Waraich, F. N. (2001b). *In vitro* anthelmintic activity of Allium sativum, Zingiber officinale, Curcurbita mexicana and Ficus religiosa. *Int. J. Agric. Biol.* 3 (4), 454–457.

Irum, S., Ahmed, H., Mukhtar, M., Mushtaq, M., Mirza, B., Donskow-Łysoniewska, K., et al. (2015). Anthelmintic activity of Artemisia vestita Wall ex DC. and Artemisia maritima L. against *Haemonchus contortus* from sheep. *Vet. Parasitol.* 212 (3-4), 451–455. doi:10.1016/j.vetpar.2015.06.028

Jabbar, A., Zaman, M. A., Iqbal, Z., Yaseen, M., and Shamim, A. (2007). Anthelmintic activity of Chenopodium album (L.) and Caesalpinia crista (L.) against trichostrongylid nematodes of sheep. *J. Ethnopharmacology* 114 (1), 86–91. doi:10.1016/j.jep.2007.07.027

Jaheed, E., Mohamed, A. H., Hassan, N. M. F., Mahran, K. M. A., Nasr, S. M., and Abou-Zeina, H. A. A. (2019). Evaluation of the curative effect of Balanites aegyptiaca fruits ethanolic extract on Haemonchosis experimentally induced in Egyptian Baladi goats: phytoanalytical, parasitological and hematological studies. *J. Parasit Dis.* 43 (4), 638–650. doi:10.1007/s12639-019-01143-1

Jia, J., Qin, Y., Zhang, L., Guo, C., Wang, Y., Yue, X., et al. (2016). Artemisinin inhibits gallbladder cancer cell lines through triggering cell cycle arrest and apoptosis. *Mol. Med. Rep.* 13 (5), 4461–4468. doi:10.3892/mmr.2016.5073

Kamaraj, C., Rahuman, A. A., Bagavan, A., Mohamed, M. J., Elango, G., Rajakumar, G., et al. (2010). Ovicidal and larvicidal activity of crude extracts of Melia azedarach against *Haemonchus contortus* (Strongylida). *Parasitol. Res.* 106 (5), 1071–1077. doi:10.1007/s00436-010-1750-0

Kamaraj, C., and Rahuman, A. A. (2011). Efficacy of anthelmintic properties of medicinal plant extracts against *Haemonchus contortus*. *Res. Vet. Sci.* 91 (3), 400–404. doi:10.1016/j.rvsc.2010.09.018

Kamaraj, C., Rahuman, A. A., Elango, G., Bagavan, A., and Zahir, A. A. (2011). Anthelmintic activity of botanical extracts against sheep gastrointestinal nematodes, *Haemonchus contortus*. *Parasitol. Res.* 109 (1), 37–45. doi:10.1007/s00436-010-2218-y

Karim, M. A., Islam, M. R., Lovelu, M. A., Nahar, S. F., Dutta, P. K., and Talukder, M. H. (2019). *In vitro* evaluation of anthelmintic activity of tannin-containing plant Artemisia extracts against *Haemonchus contortus* from goat. *J. Bangladesh Agric. Univ.* 17 (3), 363–368. doi:10.3329/jbau.v17i3.43216

Katiki, L., Chagas, A., Takahira, R. K., Juliani, H., Ferreira, J., and Amarante, A. F. T. d. (2012). Evaluation of Cymbopogon schoenanthus essential oil in lambs

experimentally infected with *Haemonchus contortus*. *Vet. Parasitol.* 186 (3-4), 312–318. doi:10.1016/j.vetpar.2011.12.003

Katiki, L. M., Araujo, R. C., Ziegelmeyer, L., Gomes, A. C. P., Gutmanis, G., Rodrigues, L., et al. (2019). Evaluation of encapsulated anethole and carvone in lambs artificially- and naturally-infected with *Haemonchus contortus*. *Exp. Parasitol.* 197, 36–42. doi:10.1016/j.exppara.2019.01.002

Katiki, L. M., Barbieri, A. M. E., Araujo, R. C., Veríssimo, C. J., Louvandini, H., and Ferreira, J. F. S. (2017b). Synergistic interaction of ten essential oils against *Haemonchus contortus in vitro. Vet. Parasitol.* 243, 47–51. doi:10.1016/j.vetpar.2017.06.008

Katiki, L. M., Gomes, A. C. P., Barbieri, A. M. E., Pacheco, P. A., Rodrigues, L., Veríssimo, C. J., et al. (2017a). *Terminalia catappa* : chemical composition, *in vitro* and *in vivo* effects on *Haemonchus contortus. Vet. Parasitol.* 246, 118–123. doi:10.1016/j.vetpar.2017.09.006

Kaur, R., and Sood, M. (1982). *In vitro* effect of anthelmintics on malic enzyme and cholinesterase of *Haemonchus contortus* (Nematoda: trichostrongylidae). *Indian J. Parasit* 6, 267–268. doi:10.1007/BF02213962

Kayani, S., Ahmad, M., Sultana, S., Khan Shinwari, Z., Zafar, M., Yaseen, G., et al. (2015). Ethnobotany of medicinal plants among the communities of Alpine and Sub-alpine regions of Pakistan. *J. Ethnopharmacology* 164, 186–202. doi:10.1016/j.jep.2015.02.004

Kerboeuf, D., Riou, M., and Guegnard, F. (2008). Flavonoids and related compounds in parasitic disease control. *Mrmc* 8 (2), 116–128. doi:10.2174/138955708783498168

Khalil, L. M., Azzam, A. M., Mohamed, H. A., Aboueldahab, M. M., Taha, H. A., and Soliman, M. I. (2016). *In Vitro* effects of the stem extracts of the plant *Calotropis Procera* on *Schistosoma mansoni* adult worms. *Egypt. J. Zool* 174 (4083), 1–14.

Krstin, S., Sobeh, M., Braun, M., and Wink, M. (2018). Anti-parasitic activities of *Allium sativum* and *Allium cepa* against *Trypanosoma b. brucei* and *Leishmania tarentolae*. *Medicines* 5 (2), 37. doi:10.3390/medicines5020037

Lacey, E., Redwin, J., Gill, J., Demargheriti, V., and Waller, P. (1990). A larval development assay for the simultaneous detection of broad spectrum anthelmintic resistance. Resistance of Parasites to Antiparasitic Drugs. Round Table Conference held at the 7th International Congress of Parasitology, Paris, France, August ,1990 .

Lachenmeier, D. W. (2010). Wormwood (*Artemisia* absinthium L.)-A curious plant with both neurotoxic and neuroprotective properties?. *J. Ethnopharmacology* 131 (1), 224–227. doi:10.1016/j.jep.2010.05.062

Lara Tf, M., Ml Bevilaqua, C., Mb de Oliveira, L., Lf Camurca-Vasconcelos, A., Viera, da. S. L., et al. (2009). *In vitro* ovicidal and larvicidal activity of *Eucalyptus globulus* essential oil on *Haemonchus contortus. Rev. Bras Parasitol. Vet.* 18, 62–66. doi:10.4322/rbpv.01803011

Lee, D. L. (1996). Why do some nematode parasites of the alimentary tract secrete acetylcholinesterase?. *Int. J. Parasitol.* 26 (5), 499–508. doi:10.1016/0020-7519(96)00040-9

Li, W., Mo, W., Shen, D., Sun, L., Wang, J., Lu, S., et al. (2005). Yeast model uncovers dual roles of mitochondria in the action of artemisinin. *Plos Genet.* 1 (3), e36. doi:10.1371/journal.pgen.0010036

Liang, L., Meng, Z., Ye, F., Yang, J., Liu, S., Sun, Y., et al. (2010). The crystal structures of two cuticle-degrading proteases from nematophagous fungi and their contribution to infection against nematodes. *FASEB j.* 24 (5), 1391–1400. doi:10.1096/fj.09-136408

Lima, E. B. C., Sousa, C. N. S., Meneses, L. N., Ximenes, N. C., Santos Júnior, M. A., Vasconcelos, G. S., et al. (2015). Cocos nucifera (L.) (Arecaceae): a phytochemical and pharmacological review. *Braz. J. Med. Biol. Res.* 48 (11), 953–964. doi:10.1590/1414-431x20154773

Lone, B. A., Bandh, S. A., Chishti, M. Z., Bhat, F. A., Tak, H., and Nisa, H. (2013). Anthelmintic and antimicrobial activity of methanolic and aqueous extracts of *Euphorbia helioscopia* L. *Trop. Anim. Health Prod.* 45 (3), 743–749. doi:10.1007/s11250-012-0283-1

Lone, B. A., Chishti, M., Bhat, F. A., Tak, H., and Bandh, S. A. (2012). *In vitro* and *in vivo* anthelmintic activity of *Euphorbia helioscopia* L. *Vet. Parasitol.* 189 (2-4), 317–321. doi:10.1016/j.vetpar.2012.04.023

Lopes, L. G., Silva, M. H., Figueiredo, A., Canuto, K. M., Brito, E. S., Ribeiro, P. R. V., et al. (2018). The intake of dry cashew apple fiber reduced fecal egg counts in *Haemonchus contortus*-infected sheep. *Exp. Parasitol.* 195, 38–43. doi:10.1016/j.exppara.2018.10.004

Mabusela, W. T., Stephen, A. M., and Botha, M. C. (1990). Carbohydrate polymers from *Aloe ferox* leaves. *Phytochemistry* 29 (11), 3555–3558. doi:10.1016/0031-9422(90)85275-k

Macedo, I. T., Bevilaqua, C. M., de Oliveira, L. M., Camurça-Vasconcelos, A. L., Morais, S. M., Machado, L. K., et al. (2012). *In vitro* activity of *Lantana camara, Alpinia zerumbet, Mentha villosa* and *Tagetes minuta* decoctions on *Haemonchus contortus* eggs and larvae. *Vet. Parasitol.* 190 (3-4), 504–509. doi:10.1016/j.vetpar.2012.07.001

Macedo, I. T., Bevilaqua, C. M., de Oliveira, L. M., Camurça-Vasconcelos, A. L., Vieira, L. d. S., Oliveira, F. R., et al. (2010). Anthelmintic effect of *Eucalyptus staigeriana* essential oil against goat gastrointestinal nematodes. *Vet. Parasitol.* 173 (1-2), 93–98. doi:10.1016/j.vetpar.2010.06.004

Macedo, I. T. F., Oliveira, L. M. B. d., André, W. P. P., Araújo Filho, J. V. d., Santos, J. M. L. d., Rondon, F. C. M., et al. (2019). Anthelmintic effect of *Cymbopogon citratus* essential oil and its nanoemulsion on sheep gastrointestinal nematodes. *Rev. Bras. Parasitol. Vet.* 28 (3), 522–527. doi:10.1590/s1984-29612019065

Machado, M., Dinis, A. M., Salgueiro, L., Custódio, J. B. A., Cavaleiro, C., and Sousa, M. C. (2011). Anti-Giardia activity of *Syzygium aromaticum* essential oil and eugenol: effects on growth, viability, adherence and ultrastructure. *Exp. Parasitol.* 127 (4), 732–739. doi:10.1016/j.exppara.2011.01.011

Maciel, M., Morais, S. M., Bevilaqua, C., Camurça-Vasconcelos, A., Costa, C., and Castro, C. (2006). Ovicidal and larvicidal activity of *Melia azedarach* extracts on *Haemonchus contortus. Vet. Parasitol.* 140 (1-2), 98–104. doi:10.1016/j.vetpar.2006.03.007

Mahmoud, O. M., Adam, S. E. I., and Tartour, G. (1979). The effects of Calotropis procera on small ruminants. *J. Comp. Pathol.* 89 (2), 251–263. doi:10.1016/0021-9975(79)90064-1

Malik, S., de Mesquita, L., Silva, C., de Mesquita, J., de Sá Rocha, E., Bose, J., et al. (2019). Chemical profile and biological activities of essential oil from *Artemisia vulgaris* L. Cultivated in Brazil. *Pharmaceuticals* 12 (2), 49. doi:10.3390/ph12020049

Mansfield, L. S., Gamble, H. R., and Fetterer, R. H. (1992). Characterization of the eggshell of *Haemonchus contortus*-I. Structural components. *Comp. Biochem. Physiol. B: Comp. Biochem.* 103 (3), 681. doi:10.1016/0305-0491(92)90390-d

Maphosa, V., and Masika, P. J. (2012). Anthelmintic screening of fractions of *Elephantorrhiza elephantina* root extract against *Haemonchus contortus. Trop. Anim. Health Prod.* 44 (1), 159–163. doi:10.1007/s11250-011-9903-4

Maphosa, V., Masika, P. J., Bizimenyera, E. S., and Eloff, J. N. (2010). *In-vitro* anthelminthic activity of crude aqueous extracts of *Aloe ferox, Leonotis leonurus* and *Elephantorrhiza elephantina* against *Haemonchus contortus. Trop. Anim. Health Prod.* 42 (2), 301–307. doi:10.1007/s11250-009-9421-9

Marie-Magdeleine, C., Hoste, H., Mahieu, M., Varo, H., and Archimede, H. (2009). *In vitro* effects of *Cucurbita moschata* seed extracts on *Haemonchus contortus. Vet. Parasitol.* 161 (1-2), 99–105. doi:10.1016/j.vetpar.2008.12.008

Marie-Magdeleine, C., Mahieu, M., D'Alexis, S., Philibert, L., and Archimede, H. (2010). *In vitro* effects of *Tabernaemontana citrifolia* extracts on *Haemonchus contortus. Res. Vet. Sci.* 89 (1), 88–92. doi:10.1016/j.rvsc.2010.01.002

Marie-Magdeleine, C., Udino, L., Philibert, L., Bocage, B., and Archimede, H. (2014). *In vitro* effects of *Musa x paradisiaca* extracts on four developmental stages of *Haemonchus contortus. Res. Vet. Sci.* 96 (1), 127–132. doi:10.1016/j.rvsc.2013.12.004

Martínez-Ortiz-de-Montellano, C., de Jesús Torres-Acosta, J. F., Fourquaux, I., Sandoval-Castro, C. A., and Hoste, H. (2019). Ultrastructural study of adult *Haemonchus contortus* exposed to polyphenol-rich materials under *in vivo* conditions in goats. *Parasite* 26. doi:10.1051/parasite/2019065

Maurer, H. R. (2001). Bromelain: biochemistry, pharmacology and medical use. *Cmls, Cel. Mol. Life Sci.* 58 (9), 1234–1245. doi:10.1007/pl00000936

Min, B. R., Pomroy, W. E., Hart, S. P., and Sahlu, T. (2004). The effect of short-term consumption of a forage containing condensed tannins on gastro-intestinal nematode parasite infections in grazing wether goats. *Small Ruminant Res.* 51 (3), 279–283. doi:10.1016/s0921-4488(03)00204-9

Minho, A., Bueno, I., Louvandini, H., Jackson, F., Gennari, S., and Abdalla, A. (2008). Effect of *Acacia molissima* tannin extract on the control of gastrointestinal parasites in sheep. *Anim. Feed Sci. Technol.* 147 (1-3), 172–181. doi:10.1016/j.anifeedsci.2007.09.016

Mohanlall, V., and Odhav, B. (2009). Furans and furanones with antimycotoxigenic activity isolated from *Warburgia salutaris* (Canellaceae). *J. Med. Plants Res.* 3 (4), 231–240.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., and Group, a. t. P. (2009). Preferred reporting Items for systematic reviews and meta-analyses: the PRISMA statement. *Ann. Intern. Med.* 151 (4), 264–269. doi:10.7326/0003-4819-151-4-200908180-00135

Molares, S., and Ladio, A. (2012). The usefulness of edible and medicinal Fabaceae in Argentine and Chilean Patagonia: environmental availability and other sources of supply. *Evid. Based Complement. Alternat Med.* 2012, 901918. doi:10.1155/2012/901918

Mondal, H., Hossain, H., Awang, K., Saha, S., Mamun-Ur-Rashid, S., Islam, M. K., et al. (2015). Anthelmintic activity of ellagic acid, a major constituent of *Alternanthera sessilis* against *Haemonchus contortus*. *Pak Vet. J.* 35 (1). 58–62.

Monglo, D., Njongmeta, L. M., Musongong, G., Ngassoum, M., and Nukenine, E. N. (2006). Evaluation of anthelmintic potential of ethanolic plant extracts from northern Cameroon against eggs and infective larvae of *Haemonchus contortus*. *J. Biol. Sci.* 6 (2), 426–433. doi:10.3923/jbs.2006.426.433

Monteiro, M. V. B., Bevilaqua, C. M. L., Palha, m. d. D. C., Braga, R. R., Schwanke, K., Rodrigues, S. T., et al. (2011). Ethnoveterinary knowledge of the inhabitants of marajó island, eastern amazonia, Brazil. *Acta Amaz.* 41 (2), 233–242. doi:10.1590/s0044-59672011000200007

Morais-Costa, F., Bastos, G. A., Soares, A. C. M., Costa, E. G. L., Vasconcelos, V. O., Oliveira, N. J. F., et al. (2016). *In vitro* and *in vivo* action of *Piptadenia viridiflora* (Kunth) Benth against *Haemonchus contortus* in sheep. *Vet. Parasitol.* 223, 43–49. doi:10.1016/j.vetpar.2016.04.002

Mwine, J. T., and Van Damme, P. (2011). Why do Euphorbiaceae tick as medicinal plants? A review of Euphorbiaceae family and its medicinal features. *J. Med. Plants Res.* 5 (5), 652–662.

Neal, M. J. (2020). *Medical pharmacology at a glance*. John Wiley & Sons.

Nery, P., Nogueira, F., Martins, E., and Duarte, E. (2010). Effects of *Anacardium humile* leaf extracts on the development of gastrointestinal nematode larvae of sheep. *Vet. Parasitol.* 171 (3-4), 361–364. doi:10.1016/j.vetpar.2010.03.043

Njoku, C. J., and Asuzu, I. U. (1998). The anthelmintic effects of the leaf extract of *Ocimum gratissimum* (L.). *Phytomedicine* 5 (6), 485–488. doi:10.1016/s0944-7113(98)80047-0

Nogueira, F. A., Fonseca, L. D., da Silva, R. B., de Paiva Ferreira, A. V., Nery, P. S., Geraseev, L. C., et al. (2012). *In vitro* and *in vivo* efficacy of aqueous extract of *Caryocar brasiliense* Camb. to control gastrointestinal nematodes in sheep. *Parasitol. Res.* 111 (1), 325–330. doi:10.1007/s00436-012-2843-8

Nouri, F., Nourollahi-Fard, S. R., Foroodi, H. R., and Sharifi, H. (2016). *In vitro* anthelmintic effect of Tobacco (*Nicotiana tabacum*) extract on parasitic nematode, *Marshallagia marshalli*. *J. Parasit Dis.* 40 (3), 643–647. doi:10.1007/s12639-014-0550-3

Nsereko, G., Emudong, P., Omujal, J., Acai, J., Kungu, J. M., Kabi, F., et al. (2019). Comparison of the efficacy of crude methanolic extracts of *Cassia occidentalis* and *Euphorbia hirta* with levamisole-HCL against gastrointestinal nematodes of economic importance to goat production in Uganda. *Trop. Anim. Health Prod.* 51 (8), 2269–2278. doi:10.1007/s11250-019-01939-6

Obici, S., Otobone, F. J., Sela, V. R. d. S., Ishida, K., Silva, J. C. d., Nakamura, C. V., et al. (2008). Preliminary toxicity study of dichloromethane extract of *Kielmeyera coriacea* stems in mice and rats. *J. Ethnopharmacology* 115 (1), 131–139. doi:10.1016/j.jep.2007.09.013

Oka, Y., Nacar, S., Putievsky, E., Ravid, U., Yaniv, Z., and Spiegel, Y. (2000). Nematicidal activity of essential oils and their components against the root-knot nematode. *Phytopathology* 90 (7), 710–715. doi:10.1094/phyto.2000.90.7.710

Oliveira, G. L., Vieira, T. M., Nunes, V. F., Ruas, M. d. O., Duarte, E. R., Moreira, D. d. L., et al. (2014). Chemical composition and efficacy in the egg-hatching inhibition of essential oil of *Piper aduncum* against *Haemonchus contortus* from sheep. *Revista Brasileira de Farmacognosia* 24 (3), 288–292. doi:10.1016/j.bjp.2014.07.004

Oliveira, L. M. B., Bevilaqua, C. M. L., Costa, C. T. C., Macedo, I. T. F., Barros, R. S., Rodrigues, A. C. M., et al. (2009). Anthelmintic activity of *Cocos nucifera* L. against sheep gastrointestinal nematodes. *Vet. Parasitol.* 159 (1), 55–59. doi:10.1016/j.vetpar.2008.10.018

Opperman, C. H., and Chang, S. (1992). Nematode acetylcholinesterases: molecular forms and their potential role in nematode behavior. *Parasitol. Today* 8 (12), 406–411. doi:10.1016/0169-4758(92)90189-9

Palacios-Landín, J., Mendoza-de Gives, P., Salinas-Sánchez, D. O., López-Arellano, M. E., Liébano-Hernández, E., Hernández-Velázquez, V. M., et al. (2015). *In vitro* and *in vivo* nematocidal activity of *Allium sativum* and *Tagetes erecta* extracts against *Haemonchus contortus*. *Turk Parazitol Derg* 39 (4), 260–264. doi:10.5152/tpd.2015.4523

Patel, D., Desai, S., Devkar, R., and Ramachandran, A. V. (2012). Acute and sub-chronic toxicological evaluation of hydro-methanolic extract of *Coriandrum Sativum* L. seeds. *EXCLI J.* 11, 566–575.

Peneluc, T., Domingues, L. F., de Almeida, G. N., Ayres, M. C. C., Moreira, E. L. T., da Cruz, A. C. F., et al. (2009). Atividade anti-helmíntica do extrato aquoso das folhas de *Zanthoxylum rhoifolium* Lam.(Rutaceae). *Rev. Bras Parasitol. Vet.* 18 (1), 43–48. doi:10.4322/rbpv.018e1008

Pessoa, L., Morais, S., Bevilaqua, C., and Luciano, J. (2002). Anthelmintic activity of essential oil of *Ocimum gratissimum* Linn. and eugenol against *Haemonchus contortus*. *Vet. Parasitol.* 109 (1-2), 59–63. doi:10.1016/s0304-4017(02)00253-4

Peter, J. W., and Chandrawathani, P. (2005). *Haemonchus contortus*: parasite problem No. 1 from tropics - polar Circle. Problems and prospects for control based on epidemiology. *Trop. Biomed.* 22 (2), 131–137.

Piza, M., Féboli, A., Augusto, J., Anjos, L., Laurentiz, A., Royo, V., et al. (2019). *In vitro* ovicidal and larvicidal activity of *Psidium cattleianum* Sabine leaves against gastrointestinal nematodes of naturally infected sheep. *Bol Ind. Anim.* 76, 1–8. doi:10.17523/bia.2019.v76.e1450

Qi, H., Wang, W., Dai, J., and Zhu, L. (2015). *In vitro* anthelmintic activity of *Zanthoxylum simulans* essential oil against *Haemonchus contortus*. *Vet. Parasitol.* 211 (3-4), 223–227. doi:10.1016/j.vetpar.2015.05.029

Raja, R. R. (2012). Medicinally potential plants of Labiatae (Lamiaceae) family: an overview. *Res. J. Med. Plant* 6 (3), 203–213. doi:10.3923/rjmp.2012.203.213

Rhoads, M. L., and Fetterer, R. H. (1994). Purification and characterization of surface-associated proteins from adult *Haemonchus contortus*. *J. Parasitol.* 80, 756–763. doi:10.2307/3283254

Ribeiro, J., Ribeiro, W., Camurça-Vasconcelos, A., Macedo, I., Santos, J., Paula, H., et al. (2014). Efficacy of free and nanoencapsulated *Eucalyptus citriodora* essential oils on sheep gastrointestinal nematodes and toxicity for mice. *Vet. Parasitol.* 204 (3-4), 243–248. doi:10.1016/j.vetpar.2014.05.026

Ribeiro, W. L. C., Andre, W. P. P., Cavalcante, G. S., de Araújo-Filho, J. V., Santos, J. M. L., Macedo, I. T. F., et al. (2017). Effects of *Spigelia anthelmia* decoction on sheep gastrointestinal nematodes. *Small Ruminant Res.* 153, 146–152. doi:10.1016/j.smallrumres.2017.06.001

Rocha, R. O., Morais, J. K. S., Oliveira, J. T. A., Oliveira, H. D., Sousa, D. O. B., Souza, C. E. A., et al. (2015). Proteome of soybean seed exudates contains plant defense-related proteins active against the root-knot nematode *Meloidogyne incognita*. *J. Agric. Food Chem.* 63 (22), 5335–5343. doi:10.1021/acs.jafc.5b01109

Rogers, W. P., and Brooks, F. (1977). The mechanism of hatching of eggs of *Haemonchus contortus*. *Int. J. Parasitol.* 7 (1), 61–65. doi:10.1016/0020-7519(77)90026-1

Roy, J. (2011). "Bulk drugs or active pharmaceutical ingredients," in *Woodhead Publishing Series in Biomedicine, An Introduction to Pharmaceutical Sciences*, Woodhead Publishing, 69–109. doi:10.1533/9781908818041.69

Sachan, A. K., Vishnoi, G., and Kumar, R. (2016). Need of standardization of herbal medicines in modern era. *ijpm* 8 (3), 300–307. doi:10.5138/09750185.1847

Sakti, A. A., Kustantinah, K., and Nurcahyo, R. W. (2018). *In Vitro* and *in Vivo* anthelmintic activities of aqueous leaf infusion of *Azadirachta indica* against *Haemonchus contortus*. *Trop. Anim. Sci. J.* 41 (3), 185–190. doi:10.5398/tasj.2018.41.3.185

Saleem, U., Ahmad, B., Ahmad, M., Erum, A., Hussain, K., and Irfan Bukhari, N. (2016). Is folklore use ofEuphorbia helioscopiadevoid of toxic effects? *Drug Chem. Toxicol.* 39 (2), 233–237. doi:10.3109/01480545.2015.1092040

Saminathan, M., Gopalakrishnan, A., Latchumikanthan, A., Milton, A., Aravind, M., Dhama, K., et al. (2015). Histopathological and parasitological study of blood-sucking *Haemonchus contortus* infection in sheep. *Adv. Anim. Vet. Sci.* 3 (2), 99–108. doi:10.14737/journal.aavs/2015/3.2.99.108

Samy, R. P., and Ignacimuthu, S. (2000). Antibacterial activity of some folklore medicinal plants used by tribals in Western Ghats of India. *J. Ethnopharmacol* 69 (1), 63–71. doi:10.1016/s0378-8741(99)00156-1

Sangster, N. C., and Gill, J. (1999). Pharmacology of anthelmintic resistance. *Parasitol. Today* 15 (4), 141–146. doi:10.1016/s0169-4758(99)01413-1

Santoro, G. F., Cardoso, M. G., Guimarães, L. G. L., Freire, J. M., and Soares, M. J. (2007). Anti-proliferative effect of the essential oil ofCymbopogon citratus(DC) Stapf (lemongrass) on intracellular amastigotes, bloodstream trypomastigotes

and culture epimastigotes of Trypanosoma cruzi (Protozoa: kinetoplastida). *Parasitology* 134 (11), 1649–1656. doi:10.1017/s0031182007002958

Selemon, M. (2018). Review on control of *Haemonchus contortus* in sheep and goat. *J. Vet. Med. Res.* 5 (5).

Silva, R. R. S., Silva, C. R., Santos, V. F., Barbosa, C. R. S., Muniz, D. F., Santos, A. L. E., et al. (2019). *Parkia platycephala* lectin enhances the antibiotic activity against multi-resistant bacterial strains and inhibits the development of *Haemonchus contortus*. *Microb. Pathogenesis* 135, 103629. doi:10.1016/j.micpath.2019.103629

Sirama, V., Kokwaro, J., Owuor, B., Yusuf, A., and Kodhiambo, M. (2015). *In-vitro* anthelmintic activity of *Vernonia amygdalina* Del.(asteraceae) roots using adult *Haemonchus contortus* worms. *Int. J. Pharmacol. Res.* 5 (1), 1–2.

Soares, A. M., Oliveira, J. T., Rocha, C. Q., Ferreira, A. T., Perales, J., Zanatta, A. C., et al. (2018). *Myracrodruon urundeuva* seed exudates proteome and anthelmintic activity against *Haemonchus contortus*. *PLoS One* 13 (7), e0200848. doi:10.1371/journal.pone.0200848

Squires, J. M., Foster, J. G., Lindsay, D. S., Caudell, D. L., and Zajac, A. M. (2010). Efficacy of an orange oil emulsion as an anthelmintic against *Haemonchus contortus* in gerbils (*Meriones unguiculatus*) and in sheep. *Vet. Parasitol.* 172 (1-2), 95–99. doi:10.1016/j.vetpar.2010.04.017

Stepek, G., Behnke, J. M., Buttle, D. J., and Duce, I. R. (2004). Natural plant cysteine proteinases as anthelmintics? *Trends Parasitol.* 20 (7), 322–327. doi:10.1016/j.pt.2004.05.003

Stepek, G., Lowe, A., Buttle, D. J., Duce, I., and Behnke, J. M. (2006). *In vitro* and *in vivo* anthelmintic efficacy of plant cysteine proteinases against the rodent gastrointestinal nematode, *Trichuris muris*. *Parasitology* 132 (5), 681–689. doi:10.1017/s003118200500973x

Tadesse, D., Eguale, T., Giday, M., and Mussa, A. (2009). Ovicidal and larvicidal activity of crude extracts of *Maesa lanceolata* and *Plectranthus punctatus* against *Haemonchus contortus*. *J. Ethnopharmacology* 122 (2), 240–244. doi:10.1016/j.jep.2009.01.014

Tariq, A., Sadia, S., Pan, K., Ullah, I., Mussarat, S., Sun, F., et al. (2017). A systematic review on ethnomedicines of anti-cancer plants. *Phytother. Res.* 31 (2), 202–264. doi:10.1002/ptr.5751

Tariq, K. A., Chishti, M. Z., Ahmad, F., and Shawl, A. S. (2008). Anthelmintic efficacy of Achillea millifolium against gastrointestinal nematodes of sheep: in vitro and in vivo studies. *J. Helminthol.* 82 (3), 227–233. doi:10.1017/s0022149x08972515

Tariq, K., Chishti, M., Ahmad, F., and Shawl, A. (2009). Anthelmintic activity of extracts of *Artemisia absinthium* against ovine nematodes. *Vet. Parasitol.* 160 (1-2), 83–88. doi:10.1016/j.vetpar.2008.10.084

Tayler, N. M., De Jesús, R., Spadafora, R., Coronado, L. M., and Spadafora, C. (2020). Antiplasmodial activity of *Cocos nucifera* leaves in *Plasmodium berghei*-infected mice. *J. Parasit Dis.*, 44, 1–9. doi:10.1007/s12639-020-01207-7

Taylor, M. A. (1990). A larval development test for the detection of anthelmintic resistance in nematodes of sheep. *Res. Vet. Sci.* 49 (2), 198–202. doi:10.1016/s0034-5288(18)31077-4

Ueda-Nakamura, T., Mendonça-Filho, R. R., Morgado-Díaz, J. A., Korehisa Maza, P., Prado Dias Filho, B., Aparício Garcia Cortez, D., et al. (2006). Antileishmanial activity of Eugenol-rich essential oil from *Ocimum gratissimum*. *Parasitol. Int.* 55 (2), 99–105. doi:10.1016/j.parint.2005.10.006

Váradyová, Z., Pisarčíková, J., Babják, M., Hodges, A., Mravčáková, D., Kišidayová, S., et al. (2018). Ovicidal and larvicidal activity of extracts from medicinal-plants against *Haemonchus contortus*. *Exp. Parasitol.* 195, 71–77. doi:10.1016/j.exppara.2018.10.009

Vargas-Magaña, J., Torres-Acosta, J., Aguilar-Caballero, A., Sandoval-Castro, C., Hoste, H., and Chan-Pérez, J. (2014). Anthelmintic activity of acetone–water extracts against *Haemonchus contortus* eggs: interactions between tannins and other plant secondary compounds. *Vet. Parasitol.* 206 (3-4), 322–327. doi:10.1016/j.vetpar.2014.10.008

Veerakumari, L., and Chitra, N. (2016). Effect of *Allium sativum* on the motility and acetylcholinesterase of *Haemonchus contortus*. *IJSR* 5 (1), 883–887. doi:10.21275/v5i1.nov152809

Wang, J., Zhang, C.-J., Chia, W. N., Loh, C. C., Li, Z., Lee, Y. M., et al. (2015). Haem-activated promiscuous targeting of artemisinin in *Plasmodium falciparum*. *Nat. Commun.* 6 (1), 1–11. doi:10.1038/ncomms10111

Wolstenholme, A. J., Fairweather, I., Prichard, R., von Samson-Himmelstjerna, G., and Sangster, N. C. (2004). Drug resistance in veterinary helminths. *Trends Parasitol.* 20 (10), 469–476. doi:10.1016/j.pt.2004.07.010

Zamilpa, A., García-Alanís, C., López-Arellano, M. E., Hernández-Velázquez, V. M., Valladares-Cisneros, M. G., Salinas-Sánchez, D. O., et al. (2019). *In vitro* nematicidal effect of *Chenopodium ambrosioides* and *Castela tortuosa* n-hexane extracts against *Haemonchus contortus* (Nematoda) and their anthelmintic effect in gerbils. *J. Helminthol.* 93 (4), 434–439. doi:10.1017/s0022149x18000433

Żarnowski, R., Żarnowska, E. D., and Kozubek, A. (2001). Alkylresorcinols in the family Fabaceae. *Acta Soc. Bot. Pol.* 70 (1), 25–29. doi:10.5586/asbp.2001.004

Zenebe, S., Feyera, T., and Assefa, S. (2017). *In vitro* anthelmintic activity of crude extracts of aerial parts of *Cissus quadrangularis* L. and leaves of *Schinus molle* L. against *Haemonchus contortus*. *Biomed. Res. Int.* 2017. 1905987. doi:10.1155/2017/1905987

Zhu, L., Dai, J., Yang, L., and Qiu, J. (2013a). Anthelmintic activity of *Arisaema franchetianum* and *Arisaema lobatum* essential oils against *Haemonchus contortus*. *J. Ethnopharmacology* 148 (1), 311–316. doi:10.1016/j.jep.2013.04.034

Zhu, L., Dai, J., Yang, L., and Qiu, J. (2013b). *In vitro* ovicidal and larvicidal activity of the essential oil of *Artemisia lancea* against *Haemonchus contortus* (Strongylida). *Vet. Parasitol.* 195 (1-2), 112–117. doi:10.1016/j.vetpar.2012.12.050

Zips, D., Thames, H. D., and Baumann, M. (2005). New anticancer agents: *in vitro* and *in vivo* evaluation. *In Vivo* 19 (1), 1–7.