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.

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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.

Keywords: medicinal plants, pharmacology, nematicidal activity, Haemonchus contortus, toxicology, ethnoveterinary, antiparasitic, anthelmintic

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, environmentally 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
plants 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):

\[
JI = \frac{c}{a + b - c}
\]

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.

**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...
| Study          | Species/compound stated in the article | Plant source                                                                 | Authenticated species | Quality control reported? | Chemical analysis reported? |
|---------------|----------------------------------------|-------------------------------------------------------------------------------|----------------------|----------------------------|----------------------------|
| Cala et al. (2012) | Melia azedaracha L                      | Not stated                                                                    | -                    | Yes                        | Yes-liquid-liquid chromatography |
|               | Trichilia clausenii C                  |                                                                              |                      |                            |                             |
| Irum et al. (2015) | Artemisia vesbita Wall ex Besser       | Collected from northern areas of Pakistan                                    | +                    | No                         | No                          |
|               | Seriphidium maritimum (L.) Poljak (=Artemisia maritima L.) |                                                                              |                      |                            |                             |
| Jaheed et al. (2019) | Balantias egyptiaca (L.) Delle | 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 | Ntselamanzi, nkonkobe municipality, eastern cape province, South Africa   | +                    | Yes                        | No                          |
| Marie-Magedeleine et al. (2014) | Musa x paradisiaca L | Guadeloupe French west indies                                               | -                    | No                         | No                          |
| Minho et al. (2008) | Acacia decurrens (J.C.Wendt.) Wild. (=Acacia mollissima Wild.) | 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.) | 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                          |
| Martinez-Ortiz-de-Montellano et al. (2019) | Lyallona latissilquum (L.) Benth. Onobrychis vicifolia Scop (=Vernonia amygdalina Del.) | 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 amygdalimum (Delile) Sch.Bip. (=Vernonia amygdalina Del.) | Not stated                                                                    | -                    | Yes                        | No                          |
| Squires et al. (2010) | Artemisia annua L                    | Appalachian farming systems research left                                     | -                    | No                         | No                          |
| Maphosa and Maska (2012) | Artemisia absinthum L               | 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 lida (farra 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 chirata (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 (=Senphidium herba-alba (Asso) Sojak) | Not stated                                                                    | -                    | Yes                        | No                          |
| Silva et al. (2019) | Parkinson platycephala Bentham         | Chapadinha, maranhao, Brazil                                                  | -                    | Yes                        | No                          | (Continued on following page)
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? |
|------------------------------|-----------------------------------------|--------------------------------------------------------------------------------|-----------------------|---------------------------|------------------------------|
| 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. Corn. 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        |
| Ferreina 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)     | Anthaea officinalis L                   | Commercial sources (AGROKARPATY, plavnica, Slovak republic and BYJNI mkeš s.r.o., cíence, Czech republic) | –                     | No                         | Yes-liquid chromatography-Mass spectrometry assay |
| Vargas-Magaña et al. (2014) | Petasites hybridus (L.) G.Gaertn., B.Mey. and Scherb | Faculty of veterinary Medicine-UDAY, 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-Shabani et al. (2008)    | Justicia adhatoda L. (=Adhatoda vasica Nees) | Harvested from sindh agriculture university (SAU), tandojam, Pakistan         | +                     | Yes                        | No                           |
| Hussien et al. (2011)       | Comandrum sativum L                     | Collected from imma town and also purchased from local market                 | +                     | No                         | No                           |
| Monglo et al. (2006)        | Annona senegalensis Pers                | Northern region of Cameroon                                                  | +                     | Yes                        | No                           |
| Ahmed et al. (2020)         | Artemisia herba-alba Asso               | Midaga-tola district                                                        | +                     | No                         | Yes-method not stated        |

(Continued on following page)
| 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.  
*Nesomer* and G.L. *Baird*  
*Perideridia gairdneri* (Hook. and Arn.) Mathias  
*Chrysothamnus viscidiflorus* Nutt.  
*Geranium viscosissimum* Fisch. and C.A. Mey  
*Mellotus abus* Medik  
*Lotis punctata* Hook.  
*Mellotus 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  
*Gynoglossum 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.  
(*=Coreopsis canadensis* (L.) Cronquist)  
*Comnus Sericea* L  
*Rubus idaeus* L  
*Actaea rubra* (Alton) Wild.  
*Symphoricarpos occidentalis* (R.Br.) Hook  
*Artemisia ludoviciana* Nutt.  
*Artemisia frigida* Willd.  
*Tanacetum vulgare* L  
*Cleome 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.)  
*Caltrops procera* (Alton.) W.T. Alton | Collected from South Dakota, North Dakota, Wyoming Montana | +          | No                        | No                           |
| Cavaicante et al. (2016)  |                                                                 | Saúde estadual do ceará                            | +                      | 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? |
|-----------------------|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------|----------------------------|------------------------------|
| Ferreira et al. (2018)| *Citrus × auranitifolia* (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.  
*Cissus quadrangularis* L.  
*Clematis brachiata* Thunb.  
*Clome gynandra* L.  
*Ficus sycomorus* L.  
*Hypoxis rigidula* Baker  
*Maerua angolensis* DC.  
*Monsonia angustifolia* E. Mey., Ex A.Rich  
*Pelargonium lurdum* (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.  
*Canna 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 Homem  
*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.) Fris and Nordal  
*Lespedeza cuneata* (Dum. Cours.) G. Don  
*Tephrosia inandensis* H.M.L. Forbes  
*Warburgia ugandensis* v Warburgia salutaris (G. Bertol.) Chev.  
*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 (=*Cucurbita mexicana* Dammann)  
*Ficus religiosa* L.  | Not stated                      | -                     | No                         | No                           |
| Study                         | Species/compound stated in the article | Plant source                                           | Authenticated species | Quality control reported? | Chemical analysis reported? |
|------------------------------|----------------------------------------|-------------------------------------------------------|-----------------------|---------------------------|-----------------------------|
| Getachew et al. (2012)       | Foeniculum vulgare Mill                | Collected from addis ababa                            | +                     | No                        | No                          |
|                              | Acalanthera schimperi (A.DC.) Schweinf |                                                       |                       |                           |                             |
|                              | Searsia pyroides (Burch.) Moffett      |                                                       |                       |                           |                             |
|                              | (=Rhus vulgaris Meikle) Rhus glabra L  |                                                       |                       |                           |                             |
|                              | Jasminum abyssinicum Hochst. ex DC.    |                                                       |                       |                           |                             |
|                              | Myrsine africana                        |                                                       |                       |                           |                             |
| 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                          |
|                              | Miosyakin and Clemants                  |                                                       |                       |                           |                             |
|                              | Moioyakina and Clemants                 |                                                       |                       |                           |                             |
|                              | (=Chenopodium ambrosioides             |                                                       |                       |                           |                             |
|                              | Castela tortuosa Liebm                  |                                                       |                       |                           |                             |
| Iqbal et al. (2005)          | Calotropis procera (Alton) W.T.Alton    | 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 Solarium tonvum Sw | Collected from the tropical region hills, Tamil nadu, India | +                     | No                        | Yes-lieberman–Burchard test |
|                              | Terminalia chebula Retz                 |                                                       |                       |                           |                             |
| Kamaraj et al. (2011)        | Catharanthus roseus (L.) G. Don Andrographis paniculata (Burmar.) Nees Anisomeles malabanica (L.) Kuntze (=Anisomeles malabanica (L.) R.Br.) | Collected from javadhu hills, tiruvannamalai district and dharmapuri district Tamil nadu, India | -                     | Yes                       | No                          |
|                              | Annona squamosa L Datura metel L Solarium tonvum Sw |                                                       |                       |                           |                             |
| 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)| Allum sativum L                        | Not stated                                            | -                     | Yes                       | No                          |
| de Oliveira et al. (2011)    | Myracrodruon urundeuva Almeao           | Collected in December 2009 in fortaleza, Ceará,Brazil | +                     | Yes                       | No                          |
|                              | Artemisia vulgaris L                    | Collected from botanical garden at the federal university of maranhão, sao luis, maranhão, Brazil | +                     | No                        | Yes-GC-MS analysis          |
| Soares et al. (2018)         | Myracrodruon urundeuva Almeao           | Purchased from arbolet seed trade (brigui, 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                        | No                          |
| Carvalho et al. (2012)       | Lippia organoides Kunth (=Lippia sidoides Cham.) Mentha x piperita L | Institute of chemistry of paulista state Embraera western. Amazon research station, Brazil | -                     | No                        | No                          |
|                              | Hura crepatans L                        | Acquired in the local market of porto velho           |                       |                           |                             |
| Katiki et al. (2012)         | Couroupita guianensis Aubl. Cymbopogon schoenanthus (L.) Spreng | Purchased from WNF Ind. and com. Ltda (sao Paulo-SP, Brazil) | -                     | No                        | No                          |
|                             |                                        |                                                       |                       |                           |                             |
|                             | (Continued on following page)           |                                                       |                       |                           |                             |
| Study                        | Species/compound stated in the article                                                                 | Plant source                                                                                                                                                                                                 | Authenticated species | Quality control reported? | Chemical analysis reported? |
|------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------------------|-----------------------------|
| Macedo et al. (2012)         | Lantana camara L.                                                                                      | Collected in the horto of medicinal plants of the universidade federal do cea ́ra in plots, state of cea ́ra, Brazil                                                                                       | +                    | No                        | Yes-GC analysis             |
|                             | Alpinia zerumbet (Pers.) B.L.Burtt and R.M.Sm.                                                       |                                                                                                 |                      |                           |                             |
|                             | Mentha arvensis L. (=Mentha villosa Becker)                                                          |                                                                                                 |                      |                           |                             |
|                             | Tagetes minuta L.                                                                                      |                                                                                                 |                      |                           |                             |
| Ribeiro et al. (2014)        | Corymbia citriodora (Hook.)                                                                          | Purchased from FERQUIIMA (vargem grande paulista, são paulo, Brazil)                                                                               | -                    | No                        | Yes- infrared spectroscopy (FTIR) |
|                             | K.D.Hill and L.A.S.Johnson (=Eucalyptus citriodora Hook.)                                            |                                                                                                 |                      |                           |                             |
| Andre et al. (2016)          | Carvacrol                                                                                             | Obtained via the acetylation of carvacrol (Sigma–Aldrich®, st. Louis, United States                                                                                       | -                    | No                        | Yes-FTIR                    |
|                             |                                                                                                       | Cerrado vegetation near montes claros city in north minas gerais state, Brazil                                                                         |                      |                           |                             |
| Morais-Costa et al. (2016)   | Lachesisdendron vriditiforu (Kunth) P.G.Ribeiro, L.P. Queiroz and Luckow (=Piptaclenia vridifoliar (Kunth) Benth.) |                                                                                                 | -                    | 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 Forsk.                                                                               | Collected along the addis ababa-butajira road and Maesa lanceolata                                                                                                                                       | +                    | No                        | No                          |
|                             | Coleus maculosus subsp.                                                                               |                                                                                                 |                      |                           |                             |
|                             | Maculosus (=Plectranthus punctatus (L.f.) L’Her.)                                                     |                                                                                                 |                      |                           |                             |
| Herath et al. (2019)         | Cryptocarya massoy (Oken) Kosterm. (=Cryptocarya ovoguineensis Teschner)                              | Not stated                                                                                       | -                    | Yes                       | Yes-HPLC                   |
|                             | Piper methysticum G.Forst                                                                           |                                                                                                 |                      |                           |                             |
| Gaínza et al. (2015)         | Citrus × aurantium L. (=Citrus × sinensis (L.) Osbeck)                                              | Not stated                                                                                       | –                    | Yes                       | Yes-GC-MS analysis          |
|                             | Melaleuca quinquenervia (Cav.) S.T.Blake                                                            |                                                                                                 |                      |                           |                             |
| de Araújo-Filho et al. (2018)| Corymbia citriodora (Hook.)                                                                          | Purchased from ferquima (sao paulo, Brazil)                                                                                                                                  | –                    | Yes                       | Yes-GC-MS analysis          |
|                             | K.D.Hill and L.A.S.Johnson (=Eucalyptus citriodora hook.)                                            |                                                                                                 |                      |                           |                             |
| Hördegen et al. (2006)       | Azadirachta indica A. Juss.                                                                          | Obtained from alfred galke GmbH, gittelde (Germany). Purchased from S.V.S. Medicinal crops dealers Pvt. Ltd., guntur (India)                                                                           | –                    | No                        | No                          |
|                             | Caesalpinia crista L                                                                                 |                                                                                                 |                      |                           |                             |
|                             | Fumaria parviflora Lam                                                                               |                                                                                                 |                      |                           |                             |
|                             | Embelia ribes Burm. 1                                                                                |                                                                                                 |                      |                           |                             |
|                             | Baccharoides anthelmintica (L.) Meonch (=Vernonia anthelmintica (L.) Willd.) Ananas comosus (L.) Merr. |                                                                                                 |                      |                           |                             |
| Camurça-Vasconcelos et al. (2007)| Croton grewioides Ball. (=Croton zehntneri Pax and K.Hoffm.)                                         | Collected in vicosa, cea ́ra state, Brazil                                                                                                                                             | +                    | No                        | Yes-GC-MS analysis          |
|                             | Lippia origanoides Kunth. (=Lippia sioides Cham.)                                                    | Purchased from PRONAT (produtos naturais) in the state of cea ́ra                                                                                                                             |                      |                           |                             |
| Hernández-Villegas et al. (2011)| Phytolacca icosandra L                                                                              | Collected in yaxcabá, yucatan, Mexico                                                                                                                                         | +                    | No                        | Yes-method not stated       |

(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? |
|-------|---------------------------------------|--------------|-----------------------|--------------------------|----------------------------|
| Eguale et al. (2011) | Croton macrostachyus Hochst. ex Delile, Bieb., Euphorbia capensis Sparrm., Vachellia nilotica (L.) P.J.H.Hurter and Mabb. (=Acacia nilotica (L.) wild. Ex. Delile) Terminalia schimperiana Hochst. (=Terminalia glaucescens Planch. ex Benth.) | Collected from their natural habitat | + | No | Yes-method not stated |
| Hamad et al. (2014) | Riccisia 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 ahnarbal area of southern kashmir valley | + | No | No |
| Piza et al. (2019) | Psidium cattleianum Sabine | Guaicabinda, 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) | Cymbopogon citratus (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. (2007) | Spigelia anthelmintica L | Ibadan, Nigeria | + | Yes | No |
| Alowanou et al. (2019) | Bidens ferruginea Benth, Combretrum glutinosum Perr. ExDC., Mitragyna inermis (Wild.) Kuntz | Abomey-calavi, kandi and comé, Benin | + | Yes | No |
| Al-Qarawi et al. (2001) | Calotropis procera (Alton.) 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.) Wild.) | Faisalabad, Punjab | + | Yes | No |
| Ademola and Idowu (2006) | Leucaena leucocephala (Lam.) de Wit | Ibadan, Nigeria | + | Yes | No |
| Barone et al. (2018) | Vaccinium macrocarpon Alton. | Not stated | − | Yes | Yes-Mass spectra method |
| Castillo-Mitre et al. (2017) | Vachellia campeachiana (Mill.) Steiger and Ebinger (=Acacia cochlaceana hamb. and bonpl. Ex wild.) | Saltire palmarios village, Mexico | + | Yes | Yes-Mass spectrometry and HPLC analysis |
| Domingues et al. (2013) | Calotropis procera (Alton.) W.T.Aiton | São paulo state, Brazil | + | Yes | No |
| Dixit et al. (2019) | Annona squamosa L, Azadirachta indica A. Juss Riccisia tabacum L | Local market, jabalpur India | − | Yes | No |
| Ferreira et al. (2016) | Thymus vulgaris L. | Ferqurma ind e com Iftda (Brazil) | + | Yes | Yes-GC-MS analysis |
| Githiori et al. (2004) | Hagenia abyssinica (Bruce) J.F.Gmel. Dodonaea viscosa subsp. angustifolia (Lf.) J.G.West (=Dodonaea angustifolia L.) Olea europaea L, Annona squamosa L, Hildebrandtia sepalsosa Rendle Azadirachta indica A. Juss Ananas comosus (L.) Merr. | Kenya and east africa | − | Yes | No |

(Continued on following page)
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
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 | Kristin 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 | Nil | Alteration of cell shape, restrict growth, collapsing cell membrane, and arrest cell division | Cavalcante et al. (2008); Tariq et al. (2009) |
| Artemisia absinthium L | Methanol 1.024 | 100 | 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 | 95 | 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 | 97.8 | Aqueous Methanol 12.5 | 98.4 | 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. (2013); Maciel et al. (2006) |
| Calotropis procera (Aiton) W.T.Aiton | Aqueous Ethyl acetate 25 | 70 | 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) |
| Castella tortuosa Liebm. | n-hexane Essential oil 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 | Egualle et al. (2007b); Hussien et al. (2011); Patel et al. (2012) |
| Cocos nucifera L | Ethyl acetate 5 | 100 | 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 | 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 nano-emulsion 1.25 | 98.4 | 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) |

(Continued on following page)
| 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 | Essential oil | 360 | No activity | 180; 360 | Nil | Inhibit vital functions, interfere with 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 | 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 with 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 | Martinez-Ortiz-de-Montellano et al. (2019); Vargas-Magaña et al. (2014); Andjani et al. (2019); Hamad et al. (2014); Iqbal et al. (2006b); Morais-Costa et al. (2016) |
| Nicotiana tabacum L | Aqueous Methanol | 25 | 77 | Aqueous Methanol | 4000 | 86.6 | 5000 | Nil | Inhibit acetylcholine, and paralysis | |
| Lachesisdendron viridi florum (Kunth) P.G.Ribeiro, L.P. Queiroz and Luckow (=Piptadenia viridiflora (Kunth) Benth.) | Aqueous Methanol | 0.075 | 100 | Aqueous Methanol | 283 | Highly effective | 203 | Nil | Inhibit enzymatic activities and metabolic processes | |
| Senichidium brevifollum (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.
\textit{sativum} L., \textit{Lippia origanoides} Kunth (syn. \textit{Lippia sidoides} Chem.), \textit{Artemisia absinthium} L., \textit{Cymbopogon citratus} (DC.) Stapf, \textit{Eucalyptus staigeriana} F. Muell. ex F.M. Bailey, \textit{Artemisia herba-alba} Asso, and \textit{Corymbia citriodora} (Hook.) K.D. Hill and L.A.S. Johnson in order of their appearance. While \textit{A. herba-alba}, \textit{C. procera}, \textit{C. citriodora}, \textit{Lysiloma latisiliquum} (L.) Benth., and \textit{Euphorbia helioscopia} L. were reported with high efficacy in vivo. Among the plants, \textit{L. viridiflorum} was found highly effective both in vitro and in vivo with no observed toxic effects. \textit{C. citriodora} was moderately toxic in vivo, but with promising nematicidal activity in vitro and in vivo. Additionally, \textit{C. procera} and \textit{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; \textit{Annona squamosa} L., \textit{Artemisia maritima} L., \textit{Artemisia capillaris} Thunb., \textit{Castela tortuosa} Liebm., \textit{L. latisiliquum}, and \textit{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 LC50 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 \textit{H. contortus}. While only 3 compounds were found to be evaluated for in vivo activity using gerbil (\textit{Meriones unguiculatus}) as an animal model. Based on minimum concentration and maximum nematcidal 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 larval development was also significant, but relatively at high concentrations i.e., 10 and 20 mg/ml, correspondingly.

Carvacrol and carvacyl acetate at 2 mg/ml showed 100% larval motility inhibition as compared to other compounds. Similarly, carvacyl 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 (Zarnowski 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 \textit{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 \textit{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 \textit{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) |
|               |            | ![1,8-Cineole chemical structure](image) |                   | 1.25    | 10.0                   | 0.63   | LDT            | 10.6       | Katiki et al. (2017b) |
|               |            | ![1,8-Cineole chemical structure](image) |                   | 2.5     | 26.6                   | 1.25   | 23.4           | Katiki et al. (2019) |
|               |            | ![1,8-Cineole chemical structure](image) |                   | 5.0     | 56.6                   | 2.5    | 33.6           | Katiki et al. (2017b) |
|               |            | ![1,8-Cineole chemical structure](image) |                   | 10.0    | 74.8                   | 5.0    | 49.2           | Katiki et al. (2017b) |
|               |            | ![1,8-Cineole chemical structure](image) |                   | 0.63    | LDT                    | 10.0   | 65.2           | Katiki et al. (2017b) |
|               |            | ![1,8-Cineole chemical structure](image) |                   | 1.25    | 23.4                   | 2.5    | 33.6           | Katiki et al. (2017b) |
|               |            | ![1,8-Cineole chemical structure](image) |                   | 5.0     | 49.2                   | 5.0    | 49.2           | Katiki et al. (2017b) |
|               |            | ![1,8-Cineole chemical structure](image) |                   | 10.0    | 65.2                   | 10.0   | 60.3           | Katiki et al. (2017b) |
| Anethole      | 1-Methoxy-4-(prop-1-en-1-yl)benzene | Produced synthetically | Essential oil     | 1.787   | EHT                    | 99     | Katiki et al. (2017b) |
|               |            | ![Anethole chemical structure](image) |                   | 0.31    | EHT                    | 6.7    | Camurça-Vasconcelos et al. (2007) |
|               |            | ![Anethole chemical structure](image) |                   | 0.62    | EHT                    | 26.6   | Katiki et al. (2017b) |
|               |            | ![Anethole chemical structure](image) |                   | 1.25    | 99.9                   | 1.25   | 99.9           | Katiki et al. (2017b) |
|               |            | ![Anethole chemical structure](image) |                   | 2.5     | 52.1                   | 2.5    | 52.1           | Katiki et al. (2017b) |
|               |            | ![Anethole chemical structure](image) |                   | 5.0     | 87.7                   | 5.0    | 87.7           | Katiki et al. (2017b) |
|               |            | ![Anethole chemical structure](image) |                   | 10.0    | 96.7                   | 10.0   | 96.7           | Katiki et al. (2017b) |
|               |            | ![Anethole chemical structure](image) |                   | 20.0    | 100                    | 20.0   | 100            | Katiki et al. (2017b) |
|               |            | ![Anethole chemical structure](image) |                   | 50      | FEC*                   | 50     | Katiki et al. (2017b) |
|               |            | ![Anethole chemical structure](image) |                   | 0.085   | EHT                    | 99     | (Continued on following page) |

*Fecal egg count was significantly reduced, decreased male length, and reproductive capacity of female after 45 days in santa ines lambs*

*The dose did not affect acquisition of parasites after pasture access and as FEC raised and body weight decreased of morada nova lambs*
### 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 | Anisandra franchelianum Engl., A. lobatum Engl./Araceae | Essential oil | 0.32 EHT | 52.6 | Zhu et al. (2013a) |
|               |                                 |                   |         | 0.63 EHT             | 65.6   |                |            |
|               |                                 |                   |         | 1.25                 | 83.4   |                |            |
|               |                                 |                   |         | 2.5                  | 93.2   |                |            |
|               |                                 |                   |         | 5.0                  | 100    |                |            |
|               |                                 |                   |         | 10.0                 | 100    |                |            |
|               |                                 |                   |         | 0.32 LDT             | 38.4   |                |            |
|               |                                 |                   |         | 0.63 LDT             | 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) |
| Essential oil | 2 LMT | 100 |
| Essential oil | 0.2 AWMT | 58.3 |

(Continued on following page)
### 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     | ![Carvacryl acetate structure](image)                                              | NA                                       | NA             | 250                   | EGP    | 57.7%         | The compound reduced 57.7% of eggs per Gram of gastrointestinal parasites including H. contortus | André et al. (2020) |
| Eugenol                        | 4-Allyl-2-methoxyphenol                          | ![Eugenol structure](image)                                                       | Ocimum grattissimum L./Lamiaceae         | Essential oil  | 8                     | EHT    | 89.3          | Andre et al. (2016)                                                   |
|                                |                                                  |                                                                                     |                                           | 2              | LMT                   | 100    |               |                                                                       |
|                                |                                                  |                                                                                     |                                           | 0.2            | AWMT                  | 100    |               |                                                                       |
| Linakool                       | 3,7-Dimethyl-1,6-octadien-3-ol                   | ![Linakool structure](image)                                                      | Arisaema francheliartum Engl., A. lobatum Engl./Araceae | Essential oil  | 0.625                 | EHT    | 58.49         | Pessoa et al. (2002)                                                  |
|                                |                                                  |                                                                                     |                                           | 1.25           | EHT                   | 76.02  |               |                                                                       |
|                                |                                                  |                                                                                     |                                           | 2.5            |                      | 94.56  |               |                                                                       |
|                                |                                                  |                                                                                     |                                           | 5              |                      | 100    |               |                                                                       |
|                                |                                                  |                                                                                     |                                           | 10             |                      | 100    |               |                                                                       |
| Thymol                         | 5-Methyl-2-(propan-2-yl)phenol                   | ![Thymol structure](image)                                                        | Lippia orphanoideus Kunth (=Lippia sidoides Cham.)/Verbenaceae | Essential oil  | 0.31                  | EHT    | 99            | Katiki et al. (2017b)                                                 |
|                                |                                                  |                                                                                     |                                           | 1.25           |                      | 93.6   |               |                                                                       |
|                                |                                                  |                                                                                     |                                           | 2.5            |                      | 98.2   |               |                                                                       |
|                                |                                                  |                                                                                     |                                           | 5.0            |                      | 33.0   |               |                                                                       |
|                                |                                                  |                                                                                     |                                           | 10.0           |                      | 73.9   |               |                                                                       |
|                                |                                                  |                                                                                     |                                           | 20.0           |                      | 99.2   |               |                                                                       |
| Citronellal                    | 3,7-Dimethylct-6-enal                            | ![Citronellal structure](image)                                                   | Corymbia citiodora (Hook.) K.D. Hill and L.A.S. Johnson (=Eucalyptus citiodora 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-triazaacyclobdecane | ![Lectin structure](image)                                                       | Pankia platyccephala Benth/ Leguminosae | Protein        | 1.2                    | LDT    | 50            | Silva et al. (2019)                                                   |
|                                |                                                  |                                                                                     |                                           | 0.31           | LDT                   | 50     |               |                                                                       |

(Continued on following page)
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 | (2R)-2-[(E)-2-phenylethenyl]-2,3-dihydropyran-6-one | Cryptocarya massey (Oken) Kosterm. (=Cryptocarya novoguineensis Teschner)/ Lauraceae | NA | 200–300 μM | LDT | IC₅₀, IC₉₀ | Herath et al. (2019) |
| Dihydrokavain | (S)-4-methoxy-2-(2-phenylethyl)-2,3-dihydropyran-6-one | Piper methysticum G. Forst./Piperaceae | NA | 207 μM | LDT | IC₅₀ | Herath et al. (2019) |
| Desmethoxyyangonin | 4-Methoxy-6-[(E)-2-phenylethenyl]pyran-2-one | P. methysticum G. Forst./Piperaceae | NA | 31.7 μM | LDT | IC₅₀ | 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 | IC₅₀ | Herath et al. (2019) |
| Carvone* | 2-Methyl-5-prop-1-en-2-ylcyclohex-2-en-1-one | Supplied by GRASP Ind. E com. (Curitiba-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) |
| Cinnamaldehyde | (E)-3-phenylprop-2-enal | Produced synthetically | Essential oil | 0.366 | EHT | 99 | Katiki et al. (2017b) |
| | | | Essential oil | 0.085 | EHT | 99 | Katiki et al. (2017b) |

(Continued on following page)
### 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 | ![Chemical Structure](image) | Produced synthetically | Essential oil | 815.16 | EHT | 99 | Katki et al. (2017b) |
| Limonene      | 1-Methyl-4-prop-1-en-2-ylcyclohexene | ![Chemical Structure](image) | Obtained from citrus peel | Essential oil | 207.56 | EHT | 50 | Katki et al. (2017b) |

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

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**FIGURE 5** | Jaccard similarity index (A) represents plants used in vitro and (B) represents plants used in vivo.
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 synthase (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 (Stepek et al., 2005). Allium sativum inhibits Acetylcholinesterase (AChE) that hydrolyzes the neurotransmitter acetylcholine. Inhibition of AChE 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 synthase (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 (Stepek et al., 2005). Allium sativum inhibits Acetylcholinesterase (AChE) that hydrolyzes the neurotransmitter acetylcholine. Inhibition of AChE leads to the accumulation of acetylcholine at the synaptic junction and disrupting the neuromuscular transmission which causes muscle paralysis.

**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 AChE leads to the accumulation of acetylcholine at the synaptic junction and disrupting the neuromuscular transmission which causes muscle paralysis.
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 (Rakkali 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 monoterpenes, 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 affect 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 anthelmina* 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 (Hennesy, 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 activities 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 compounds 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 Bhattacharryya, 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 (Aratijo-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 clausennii* C. DC., *Croton macrostachyus* Hochst ex Delile, *Lavandula officinalis* (Chaix and Kiti), *Colesus maculosus* subsp. edulis (Vatke) A.J.Paton (*Plectranthus punctatus* (L.f) L’Her.), *Maesa lancifolata* 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/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 and Supplementary Material, further inquiries can be directed to the corresponding authors.

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### AUTHOR CONTRIBUTIONS

MA and RA conceptualized the idea. RA, MR, and SM searched the literature and drafted the manuscript. RA, MR, SM, SN, and SA drafted the figures and tables. MA, SNK, and SM supervised the whole process, provided comments on the initial draft and helped in editing. All authors critically revised the manuscript and approved the final version.

### 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.
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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