



Measures to Control *Haemonchus contortus* Through Plant Mediated Green Technology

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Abstract

Haemonchus contortus is the most important parasite of the small ruminants. It causes diarrhea, bottle jaw, and edema, leading to anemia as a result, the production of milk and meat is reduced, causing significant economic and productive losses for people who are entirely dependent on livestock for their livelihood. Conventional methods such as pasture management and chemical anthelmintics are not very efficient against this problem, as the widespread use of chemical anthelmintics has led to the emergence of drug resistance. Therefore, it is essential to identify novel effective anthelmintics against drug-resistant strain. Plant-mediated anthelmintics are good alternatives against *H. contortus* and arise the interest of several researchers worldwide. This article extensively reviews the present state of knowledge regarding various plant extracts and their derivatives used against the gastrointestinal nematode *H. contortus* by several researchers.

Keywords: Anthelmintics, Drug Resistance, Livestock, Parasite, Plant Mediated.

Introduction

India has a rich tradition of animal husbandry, playing a vital role in the country's agricultural economy. Livestock farming not only provides a source of income but also contributes significantly to the nutritional security of the nation. With a significant portion of the rural population dependent on animal husbandry for their livelihood, it serves as a crucial sector for employment generation. According to the Department of Animal Husbandry and Dairying Annual Report 2022-2023 livestock sector alone contributes approximately 4.11% to the national GDP and about 25.6% to the agricultural GDP. As per 20th Livestock Census in the country, there are about 303.76 million bovines (cattle, buffalo, mithun and yak), 74.26 million sheep, 148.88 million goats, 9.06 million pigs, and about 851.81 million poultry. (Annual report 2022-2023). In the Indian economy, the livestock sector serves as a vital safeguard against the uncertainties of crop failure, offering steady year-round income and ensuring access to nutritious food.

Haemonchosis, caused by *Haemonchus contortus* (Rud., 1803), a gastrointestinal parasite belonging to the family Trichostrongylidae of phylum Nematoda, is the prevailing issue among small ruminants in regions where animal husbandry is a significant practice. It affects a majority of tropical, sub-tropical, and temperate countries worldwide. The adult parasite attaches itself to the host's gut and feeds on blood in the stomach (abomasum), exerting a significant impact on the population of small ruminants. This impact includes damage to gastric function, hemorrhagic gastroenteritis, diarrhea, depression of mineral levels, edema (manifesting as bottle jaw), all of which contribute to weight loss, reduced milk production, decreased meat and wool production, and frequent mortality (Fox, 1993). In Kenya alone, annual treatments for *H. contortus* have been estimated to amount to approximately 26 million USD. In the Republic of South Africa, this figure rises to 46 million USD, and in India, it reaches a staggering 103 million USD. Such substantial expenditures underscore the importance of this helminth (Arsenopoulos, 2021). Consequently, it leads to significant economic and productivity losses for livestock breeders in developing countries, such as India, where extensive grazing practices are prevalent (Waller, 1997).

Various approaches have been employed to combat this problem. The two most common conventional methods utilized are pasture management techniques and the administration of chemical anthelmintics to control gastrointestinal nematodes. Pasture management plays a pivotal role in controlling gastrointestinal nematodes in small ruminants. One of the most effective techniques is rotational grazing. Rotational grazing involves dividing pastures into smaller paddocks and rotating the animals between them at regular intervals. This method helps break the nematode life cycle by allowing pastures to rest and preventing overgrazing, which reduces the parasite's access to host animals. Rotational grazing can be integrated with other pasture management practices to enhance its effectiveness. These may include the strategic use of alternative forages, such as legumes and browse species, which have been shown to have natural anthelmintic properties. Additionally, practices like mixed-species grazing and pasture resting periods can further reduce parasite burdens in small ruminant herds. While rotational grazing offers significant benefits in controlling gastrointestinal nematodes, its implementation may face certain challenges and considerations. Adequate pasture infrastructure, including fencing and water access, is essential for successful rotational grazing systems. Moreover, careful planning and monitoring are required to ensure optimal stocking densities and grazing rotations, considering factors such as pasture growth rates, weather conditions, and animal nutritional requirements. Furthermore, farmer education and extension services play a crucial role in promoting the adoption of sustainable pasture management practices and supporting farmers in overcoming potential barriers.

However, the widespread and excessive use of chemical anthelmintics has resulted in the development of drug resistance. The first case of resistance to anthelmintics was accurately documented by Drudge *et al.* (1964). Subsequently, numerous reports have highlighted anthelmintic resistance to all three broad-spectrum families of anthelmintics, namely Benzimidazole, Imidazothiazole, and Ivermectin, against *H. contortus* (Rolfe *et al.*, 1990; Swarnkar *et al.*, 1999; Chandra *et al.*, 2015). Consequently, anthelmintics derived from plant sources can offer environmentally safer and alternative measures for the treatment of gastrointestinal infections (Akhtar *et al.*, 2000; Kamaraj *et al.*, 2011). In the biological control program of *H. contortus*, the utilization of plant extracts emerges as the most effective approach. This article provides an extensive review of the current understanding regarding different plant extracts and their derivatives, such as essential oils, which have been studied by various researchers for their efficacy against *H. contortus*. The findings are summarized in Table 1 and Table 2. Furthermore, the article delves into the mode of action of these plant extracts and discusses other relevant parameters associated with their use.

Anthelmintic Resistance

The doses of drugs that would normally be lethal to organisms of the same species and stage are referred to as the lethal dose for that species. The organism's ability to survive against such doses is commonly known as drug resistance. According to Coles *et al.* (2006), drug resistance can be defined further based on drug concentrations that inhibit certain aspects of development or motility in 50% or 99% of the population during in-vitro dose-response experiments with free-living life stages. Among trichostrongylid nematodes, *Haemonchus contortus* has been extensively studied for anthelmintic resistance. The significant economic impact of this species arises from its ability to develop resistance to all major anthelmintic drugs.

Anthelmintic resistance has become a significant concern in the management of *Haemonchus contortus*, the barber's pole worm, which affects small ruminants like sheep and goats. This parasite has developed resistance to multiple classes of anthelmintics, including benzimidazoles, macrocyclic lactones, imidazothiazoles, and tetrahydropyrimidines. The emergence of resistance has severely limited the effectiveness of these anthelmintics in controlling *Haemonchus contortus* infections, posing challenges for livestock producers worldwide.

Mechanisms of Anthelmintic Resistance

Genetic Mutations: Resistance is primarily driven by genetic mutations that confer survival advantages to worms exposed to anthelmintics. These mutations can affect drug targets, drug metabolism, or drug efflux mechanisms. Kaminsky *et al.* (2008) studied the development of resistance to amino-acetonitrile derivatives (AADs), specifically monepantel, in *Haemonchus contortus*. They discovered that mutations in genes encoding nicotinic acetylcholine receptors, such as Hco-des-2H, Hco-acr-23H, and Hco-MPTL-1, were associated with monepantel resistance. Mutations in these receptor genes were identified in experimental *H. contortus* strains exposed to high concentrations of monepantel. These mutations alter the receptor structure, reducing monepantel binding and effectiveness. The resistance-associated mutations were detected in *H. contortus* strains following exposure to high doses of monepantel, indicating that such exposure can select for resistant individuals.

Selection Pressure: Frequent and improper use of anthelmintics exerts strong selection pressure, encouraging the proliferation of resistant strains.

Biological Mechanisms

Altered Drug Target Sites: Changes in the structure of drug target sites (e.g., β -tubulin gene mutations for benzimidazoles) reduce drug binding and efficacy. The study by Kwa *et al.* (1994 and 1995) provided significant insights into the mechanism of benzimidazole resistance in *Haemonchus contortus*. These researchers used *Caenorhabditis elegans* as a model organism to demonstrate the role of specific genetic mutations in conferring resistance. The researchers transferred the gene encoding isotype 1 of β -tubulin from a benzimidazole-sensitive *H. contortus* to a benzimidazole-resistant *C. elegans* (Kwa *et al.*, 1994 & 1995). This gene transfer rendered the resistant *C. elegans* susceptible to benzimidazoles, indicating that the sensitive β -tubulin gene restored drug efficacy. The study identified a specific mutation in the β -tubulin gene where the amino acid tyrosine (Tyr) at position 200 is replaced by phenylalanine (Phe). This tyrosine to phenylalanine substitution at position 200 (Tyr200Phe) was shown to be crucial for benzimidazole resistance in *H. contortus*. When the Tyr200Phe mutation was reversed through in vitro mutation (changing phenylalanine back to tyrosine), the *H. contortus* strain lost its resistance to benzimidazoles, becoming susceptible again. This demonstrated that the presence of tyrosine at position 200 in the β -tubulin gene is essential for the effective binding of benzimidazoles, whereas its replacement with phenylalanine disrupts this binding, leading to resistance. Kwa *et al.*'s research provided a clear demonstration of how a single amino acid change in the β -tubulin gene can determine the susceptibility or resistance of *Haemonchus contortus* to benzimidazoles. This finding is crucial for both understanding the molecular basis of anthelmintic resistance and for developing strategies to mitigate its impact in parasitic nematode control programs.

Silvestre *et al.* (2009) proposed several hypotheses regarding the origin of β -tubulin resistance alleles in *Haemonchus contortus* populations. Their study utilized both neutral microsatellite markers and specific anthelmintic resistance markers to explore the genetic diversity and evolutionary dynamics of these resistance alleles. One hypothesis is that the β -tubulin resistance alleles may have originated from a single mutational event. This suggests that the resistance allele could have arisen once and then spread through *H. contortus* populations via

gene flow or selection pressure. Another possibility is that new resistance alleles could be generated by recurrent mutations in isolated populations. This indicates that isolated populations may independently develop resistance due to similar selective pressures, leading to multiple origins of the resistance allele. A third hypothesis is that existing resistance alleles could be introduced into different populations through the movement of animals or other mechanisms. This means that resistant alleles could spread between populations due to the movement of resistant parasites carried by livestock. Microsatellite Markers were used to assess the genetic diversity and structure of *H. contortus* populations, providing insights into gene flow and population connectivity and Anthelmintic Resistance Markers for resistance, particularly the β -tubulin gene mutations, helped identify and track the presence of resistance alleles in different populations. Silvestre *et al.*'s work highlights the complexity of the genetic mechanisms underlying anthelmintic resistance. Their hypotheses underscore the potential for both independent evolution and the spread of resistance alleles through population interactions. This understanding is crucial for developing effective management strategies to combat resistance.

Increased Drug Efflux: Upregulation of P-glycoproteins and other efflux pumps can remove drugs from the parasite's cells. Lifschitz *et al.* (2010) investigated the role of P-glycoprotein (P-gp) inhibitors in enhancing the efficacy of macrocyclic lactones against *Haemonchus contortus* strains that had developed resistance to these drugs. P-glycoproteins are efflux pumps that can expel drugs from the cells of *H. contortus*, reducing the drugs' effective concentration and thereby contributing to resistance. Inhibiting these P-glycoproteins could potentially increase the intracellular concentration of macrocyclic lactones, restoring their efficacy against resistant worms. The study found that the use of P-glycoprotein inhibitors significantly increased the efficacy of macrocyclic lactones against resistant *H. contortus* strains in sheep. This combination approach led to higher mortality rates in the resistant *H. contortus* populations compared to the use of macrocyclic lactones alone. The findings of Lifschitz *et al.* (2010) suggest that P-glycoprotein inhibitors can significantly enhance the efficacy of macrocyclic lactones against resistant *Haemonchus contortus* strains. This approach offers a valuable tool for managing anthelmintic resistance, providing a way to restore the effectiveness of existing drugs and improve the outcomes of parasite control programs in sheep and potentially other ruminants.

Metabolic Detoxification: Enhanced metabolic processes can neutralize drugs before they reach their target sites. Rothwell and Sangster's (1997) research on closantel resistance in *Haemonchus contortus* provided critical insights into the mechanisms underlying this resistance. Their findings highlight several factors contributing to the reduced efficacy of closantel in resistant strains. Both closantel-susceptible and -resistant *H. contortus* strains were unable to metabolize closantel in vitro and in vivo. This indicates that metabolic degradation of closantel is not a factor in resistance. The researchers used radio-labelled closantel to track the drug's concentration within the helminths after administration to sheep. They found that closantel-resistant strains had lower concentrations of the drug compared to susceptible strains. This is due to the strong binding of closantel to albumins in the intestine of the helminth affected its bioavailability. This binding likely reduced the free drug concentration available to exert its anthelmintic effect and Resistant worms showed increased excretion of closantel, further decreasing the drug's effective concentration within the parasite. These findings emphasize the need for comprehensive strategies that address these specific resistance mechanisms to effectively manage and control *H. contortus* in sheep.

Haemonchus contortus, as the most extensively studied trichostrongylid nematode in terms of anthelmintic resistance, has shown remarkable resistance to all major drug classes. Consequently, the resistances demonstrated by this species have had a significant worldwide economic impact. Additionally, this species has been subject to extensive study due to its biology and physiology, which make it a suitable experimental model (Gilleard, 2006, 2013). The emergence of resistance typically occurs within 10 years of introducing each drug group. During the 1990s and early 2000s, the control of this parasite became more challenging with the appearance of isolates exhibiting multidrug resistance, meaning resistance to three or more different anthelmintic drug classes (Green *et al.*, 1981; van Wyk and Malan, 1988; Echevarria *et al.*, 1991, 1996; Eddi *et al.*, 1996; Maciel *et al.*, 1996; Nari *et al.*, 1996; Love *et al.*, 2003; Cezar *et al.*, 2010). Furthermore, resistance to the most recently introduced group, the amino-acetonitrile derivatives (AADs) (monepantel), has been reported in *H. contortus* (Mederos *et al.*, 2014; Van de Bron *et al.*, 2015). The anticipated increase in prevalence and severity of resistances in field isolates of this species to the available drugs will pose challenges for producers worldwide in controlling *H. contortus*. To maintain the ability to control this parasite until new drugs become available, it is crucial to implement comprehensive and strategic approaches.

The emergence of anthelmintic resistance highlights the urgent need for alternative strategies. Integrated parasite

management approaches are being explored, incorporating a combination of different anthelmintics, strategic deworming protocols, and non-chemical control measures. These measures include optimizing pasture management, promoting genetic selection for resistance traits, and exploring novel approaches such as vaccines and natural compounds with anthelmintic properties.

Why Plant Mediated Compound Use as Anthelmintics?

The use of medicinal plants as anthelmintics has a long history dating back to ancient times. However, the advent of chemical anthelmintics, such as benzimidazoles, levamisole, ivermectin, and others, led to a decline in the use of medicinal plants. Unfortunately, the excessive use of these chemical anthelmintics resulted in the emergence of drug-resistant strains of parasites.

In contrast, plants possess a diverse array of chemical compounds, many of which exhibit medicinal and anthelmintic properties. The vast floral biodiversity offers promising alternative approaches in the realm of biological control management, promoting the utilization of safer botanical anthelmintics as a sustainable means of parasite control. Notably, plant-derived anthelmintics consist of complex blends of chemical compounds, in contrast to the single active compounds found in chemical anthelmintics. This complexity reduces the likelihood of parasites developing resistance to botanical substances. The botanical kingdom encompasses over 2,000 identified plant species that produce chemical factors and metabolites effective against various pests, making them valuable in pest control management programs worldwide. Researchers from diverse regions have extensively explored the use of plant extracts and their metabolites, employing different extraction methods, as potent anthelmintics (Maciel *et al.*, 2006; Adamu *et al.*, 2013).

Plant Mediated Compound Used as Anthelmintics

Throughout ancient times, plants and their derivatives were extensively utilized as anthelmintics. However, with the development of various chemical anthelmintics, the use of plant-based alternatives decreased. Unfortunately, the excessive use of chemical anthelmintics led to the emergence of drug-resistant strains of parasites. In response, researchers worldwide have screened numerous plant species for their potential anthelmintic properties. Various secondary compounds or metabolites, known as phytochemicals, are synthesized by plants as a defense mechanism against environmental factors that can impact their growth. These phytochemicals encompass diverse groups such as alkanes, alkenes, simple aromatics, steroids, terpenoids, alkaloids, phenolics, and essential oils. Interestingly, several researchers have previously reported on the anthelmintic properties of these phytochemicals (Carvalho *et al.*, 2012; Akkari *et al.*, 2014).

For instance, Iqbal *et al.* (2001) explored the anthelmintic potential of four different plants against gastrointestinal nematodes. These plants included *Allium sativum* (garlic, bark), *Zingiber officinale* (ginger, rhizome), *Cucurbita mexicana* (whole fruits), and *Ficus religiosa* (peepal, bark). *Allium sativum* (garlic, bark) contains sulfur-containing compounds such as allicin, which have been shown to possess antimicrobial and anthelmintic properties. Ginger contains bioactive compounds like gingerols and shogaols, known for their anti-inflammatory, antimicrobial, and anthelmintic effects. The bark of the *Ficus religiosa* tree contains tannins and flavonoids, which have various medicinal properties, including anthelmintic effects. The findings suggest that these plant extracts can serve as natural alternatives to synthetic anthelmintics, potentially reducing the risk of drug resistance in nematodes. Eguale and Giday (2009) conducted an in-depth study to evaluate the anthelmintic potential of extracts from three plants—*Lawsonia inermis*, *Jatropha curcas* (seeds), and *Chenopodium ambrosioides*—against *Haemonchus contortus*. *Lawsonia inermis* contains a variety of bioactive substances, including lawsone (2-hydroxy-1,4-naphthoquinone), flavonoids, tannins, and essential oils. Lawsone is particularly noted for its antimicrobial and antifungal properties. The study showed that extracts from the leaves and bark of *Lawsonia inermis* exhibited significant anthelmintic activity against *H. contortus*. The effectiveness was likely due to the combined action of its various bioactive compounds, particularly lawsone. While the precise mechanism was not fully elucidated, it is suggested that these compounds might interfere with the energy metabolism and structural integrity of the nematodes, leading to their death. The seeds of *Jatropha curcas* are rich in phorbol esters, diterpenoids, and other potent compounds. Phorbol esters are known for their strong biological activity, including antitumor and insecticidal properties. The anthelmintic activity is likely due to the toxic effects of the phorbol esters on nematode cells, disrupting their physiological processes and leading to paralysis or death. *Chenopodium ambrosioides* contains compounds such as ascaridole, isoascaridole, and other monoterpenoids, which have strong anthelmintic and insecticidal properties. he

presence of ascaridole, a known anthelmintic compound, is a major contributor to this effectiveness. The anthelmintic activity of *Chenopodium ambrosioides* is thought to involve the disruption of the nematode's nervous system and metabolic pathways, leading to immobilization and death.

Similarly, Eguale *et al.* (2011) conducted a study to assess the anthelmintic potential of five different plants against *Haemonchus contortus*. The plants included *Albizia schimperiana* (stem bark), *Leucas martinicensis*, *Rumex abyssinicus*, *Leonotis ocymifolia*, and *Senna occidentalis*. Each plant exhibited significant anthelmintic potential against the nematode parasite, attributed to their unique bioactive compounds. For instance, the stem bark of *Albizia schimperiana* contains saponins, tannins, flavonoids, and triterpenoids, while *Senna occidentalis* is rich in anthraquinones, saponins, and flavonoids. These compounds likely disrupt the cellular structures and metabolic processes of *H. contortus*, leading to parasite death or immobilization. The findings suggest that these plant extracts could serve as effective alternatives to synthetic anthelmintics, especially in light of increasing drug resistance. Adamu *et al.* (2013) studied 13 different plants from various families to assess their anthelmintic potential against *H. contortus*. Fouche *et al.* (2016) investigated the anthelmintic efficacy of acetone extracts derived from 14 diverse plant species against *Haemonchus contortus*. This research aimed to expand the understanding of natural remedies' potential in combating parasitic infections, particularly in livestock. By testing a broader range of plant extracts, the study sought to identify additional candidates with potent anthelmintic properties. The extracts were obtained from various parts of the plants, including leaves, stems, roots, and seeds, each potentially harboring distinct bioactive compounds. The findings of the study shed light on the diverse sources of natural anthelmintics and their potential to serve as alternatives or complements to synthetic drugs.

Furthermore, researchers have also investigated the anthelmintic potential of essential oils derived from various plants. In their study, Katiki *et al.* (2011) delved into the exploration of essential oils extracted from three distinct plant species—*Cymbopogon schoenanthus*, *Cymbopogon martini*, and *Mentha piperita*—as potential anthelmintic agents against the gastrointestinal nematode *Haemonchus contortus*. The selection of these plant species was informed by their known bioactive constituents and traditional uses in folk medicine, hinting at their potential medicinal properties. Essential oils are complex mixtures of volatile compounds, including terpenes, phenolic compounds, and other organic molecules, which are known for their diverse biological activities. These compounds often exhibit antimicrobial, antifungal, and anthelmintic properties, making them attractive candidates for therapeutic applications. The study likely involved the extraction of essential oils from different parts of the plants, such as leaves, stems, or flowers, where the concentration of bioactive compounds is typically highest. These extracts were then subjected to screening assays to evaluate their anthelmintic activity against *H. contortus*. Macedo *et al.* (2013) studied the anthelmintic potential of essential oils extracted from four different plants against *H. contortus*. These studies collectively highlight the extensive research conducted on plant extracts and essential oils, showcasing their promising anthelmintic potential against the deadly parasite *H. contortus*.

Anthelmintic Potential of Plant Metabolites: A Pathway to Effective Parasite Control.

In the quest for effective anthelmintic treatments, plant metabolites have emerged as promising candidates due to their diverse bioactive properties. However, the anthelmintic activity of these compounds is influenced by various factors, including plant species, extraction methods, geographical location, and specific plant parts used. Understanding these factors is essential for maximizing the potential of plant-based anthelmintics and overcoming the challenges posed by drug-resistant parasites. Different parts of plants, such as leaves, fruits, bark, stems, Families and roots varying concentrations of active ingredients. Moreover, variations in the concentration of these bioactive compounds exist not only between different parts of the same plant but also among different plant species within the same geographical region. This intricate variability underscores the importance of carefully selecting plant parts for extraction and recognizing the unique bioactive potential of each plant species.

Numerous plant families have been extensively studied for their anthelmintic properties. Some notable plant families include Solanaceae, Asteraceae, Labiatae, Miliaceae, Apocynaceae, and Rutaceae, which have been widely used as anthelmintics (Table 1 and Table 2). The Solanaceae family encompasses a diverse group of plants with anthelmintic properties. Among its members, plants like *Solanum nigrum* (black nightshade) and *Datura stramonium* (jimsonweed) have been traditionally used as anthelmintics in various cultures. These plants contain alkaloids such as solanine and atropine, which are believed to have anthelmintic effects. Additionally, *Withania somnifera* (ashwagandha) is another notable member of this family known for its broad medicinal properties, including potential anthelmintic activity. Plants from the Asteraceae family are known for their diverse medicinal properties,

including anthelmintic effects. *Artemisia absinthium* (wormwood) and *Tanacetum vulgare* (tansy) are well-known members of this family used as anthelmintics. They contain bioactive compounds such as sesquiterpene lactones and flavonoids, which exhibit anthelmintic activity. Additionally, *Chrysanthemum cinerariifolium* (pyrethrum) and *Artemisia annua* (sweet wormwood) are also used traditionally for their anthelmintic properties. The Lamiaceae family includes herbs renowned for their aromatic properties and medicinal uses. *Mentha piperita* (peppermint) and *Thymus vulgaris* (thyme) are notable members with anthelmintic properties. They contain essential oils rich in compounds like menthol and thymol, which possess anthelmintic activity. Additionally, *Ocimum basilicum* (basil) and *Rosmarinus officinalis* (rosemary) are also used for their potential anthelmintic effects due to their essential oil content. Although primarily known for their role as grasses, some members of the Poaceae family exhibit anthelmintic properties. *Cymbopogon citratus* (lemongrass), *Cymbopogon martinii* (palmarosa), *Cymbopogon flexuosus* (east Indian lemongrass), and *Cymbopogon winterianus* (citronella grass) are examples of grasses rich in essential oils with potential anthelmintic activity. These essential oils contain compounds like citral and geraniol, which have been studied for their anthelmintic effects. Plants from the Apocynaceae family are known for their diverse medicinal properties, including anthelmintic activity. *Carissa carandas* (karonda) and *Calotropis procera* (milkweed) are prominent members of this family used traditionally as anthelmintics. They contain bioactive compounds such as alkaloids and cardiac glycosides, which are believed to possess anthelmintic properties. Additionally, *Asclepias syriaca* (common milkweed) and *Vinca minor* (periwinkle) are also used for their potential anthelmintic effects. These examples illustrate the diversity of plant families with known anthelmintic properties and the range of bioactive compounds they contain. Further research into the specific mechanisms of action and efficacy of these plants could lead to the development of novel anthelmintic treatments.

Alkaloids, which affect the nervous system of invertebrates and are traditionally used as insect repellents, are obtained from various members of the Fabaceae, Solanaceae, Berberidaceae, and Ranunculaceae families (Rattan, 2010). The table highlights the testing of various *Artemisia* species against gastrointestinal nematodes by several researchers, with varying LC_{50} values (Table 1). Thus, the efficacy of secondary metabolite extracts from the botanical world against *Haemonchus contortus* not only depends on the plant family but also varies significantly based on the specific plant species, plant parts used, age of the plant parts (young, mature, or senescent), and the solvent employed during extraction. In this review, 165 plant types belonging to 57 different families were identified for their use against *H. contortus*. Prominent families include Asteraceae, Lamiaceae, Fabaceae, Myrtaceae, Meliaceae, and Rutaceae, which collectively account for approximately 50% of the total plants used against *H. contortus* (Figure 1). Plants from the Asteraceae, Lamiaceae, and Fabaceae families have been utilized in both diets and medicinal practices for centuries. Despite their extensive variety, most members of these families share a similar chemical makeup. For instance, all species within these families serve as rich sources of inulin, a natural polysaccharide known for its potent prebiotic properties. Additionally, these plants exhibit robust qualities such as antioxidants, anti-inflammatory agents, anthelmintics, antiviral and antimicrobial agents, as well as properties that aid in diuresis and wound healing. These therapeutic effects can be attributed to a spectrum of phytochemical compounds they contain, including polyphenols, phenolic acids, flavonoids, acetylenes, and triterpenes (Rolnik and Olas 2021).

The extraction of active biochemicals from plants is a complex process that hinges significantly on the choice of solvent, which must align with the polarity of the target compounds. This is because the principle of "like dissolves like" dictates that non-polar solvents are best suited for extracting non-polar compounds, while polar solvents are ideal for extracting polar compounds. Non-polar solvents, such as hexane and petroleum ether, are typically used to extract non-polar compounds from plants. Essential oils, which consist of volatile, non-polar molecules like terpenes, phenolic compounds, and some alkaloids, are prime examples. These solvents are highly effective at dissolving and isolating non-polar substances due to their similar chemical nature. The extraction process involves macerating the plant material in the solvent, which allows the non-polar compounds to dissolve into the solvent. The resulting solution is then subjected to processes like distillation to separate and purify the essential oils. This method is preferred for its efficiency in capturing the full spectrum of aromatic and medicinal components of the plant's essential oils. Conversely, polar solvents such as water, ethanol, and methanol are used to extract polar compounds. These compounds include higher molecular weight substances such as proteins, polysaccharides, tannins, and flavonoids. Water, being a highly polar solvent, is particularly effective in extracting these hydrophilic molecules. The process typically involves soaking or boiling the plant material in water, which allows the polar compounds to leach out. Ethanol and methanol are also commonly used, either in pure form or as mixtures with water, to optimize the extraction of certain bioactive compounds that may not be fully soluble in water alone. These polar solvents can penetrate the plant cell walls, dissolving and extracting compounds like phenolic acids,

glycosides, and other water-soluble substances.

The efficiency of extraction is greatly influenced by the polarity of the solvent. For instance, when extracting alkaloids, which can vary in polarity, a combination of solvents might be employed. An initial extraction with a non-polar solvent might be followed by a polar solvent to ensure all components are effectively extracted. Similarly, flavonoids, which are often present in glycosylated forms, are best extracted using polar solvents like ethanol or methanol, which can dissolve these complex molecules. In some cases, a sequential extraction method using solvents of increasing polarity might be utilized to ensure a comprehensive extraction of all bioactive compounds from the plant material. For example, an extraction process might start with a non-polar solvent to isolate essential oils and other non-polar compounds, followed by a polar solvent to extract remaining polar compounds. This method ensures that a wide range of biochemicals, from non-polar to highly polar, are efficiently extracted. Various extraction methods, such as maceration, percolation, Soxhlet extraction, and supercritical fluid extraction, can be employed depending on the nature of the plant material and the desired compounds. Each method has its advantages and is chosen based on factors such as efficiency, cost, and the thermal stability of the compounds. For example, supercritical fluid extraction, often using supercritical CO₂, is a versatile technique that can be adjusted for polarity by modifying the pressure and temperature, allowing for the selective extraction of both non-polar and polar compounds. The extracted compounds have diverse applications in pharmaceuticals, nutraceuticals, cosmetics, and food industries. For pharmaceutical applications, ensuring the purity and bioactivity of the extracted compounds is critical, which requires careful selection of solvents and extraction methods. In the food industry, solvent safety and residue levels must be considered, especially when using solvents like hexane. Non-polar solvents are ideal for extracting non-polar compounds such as essential oils, while polar solvents are best for extracting polar compounds like proteins and polysaccharides. Understanding the chemical nature of both the target compounds and the solvents is essential for optimizing the extraction process, ensuring maximum yield and purity of the bioactive constituents.

Studies have shown that solvents with higher polarity, such as aqueous/steam distillation or moderately polar solvents like methanol, chloroform, and ethyl acetate, have yielded promising results. However, even solvents with lower polarity, such as hexane or petroleum ether, have shown good results in various bioassays. Therefore, the choice of solvent can significantly impact the chemo-profile of the plant species and the potency of the extracted plant compounds (Assis *et al.*, 2003; Maciel *et al.*, 2006). Overall, the anthelmintic activity of plant metabolites is influenced by multiple factors, including plant species, plant part used, geographical location, and extraction method.

Unraveling the factors that influence the anthelmintic potential of plant metabolites provides valuable insights for harnessing their therapeutic properties. With plant-specific variations, exploring diverse plant families, and understanding the dynamics of extraction, researchers can pave the way for effective parasite control. By capitalizing on the rich repertoire of bioactive compounds in plants, we can develop novel anthelmintic strategies that combat drug resistance and promote global health. Continued research in this field promises exciting breakthroughs in the quest for sustainable and efficient anthelmintic solutions.

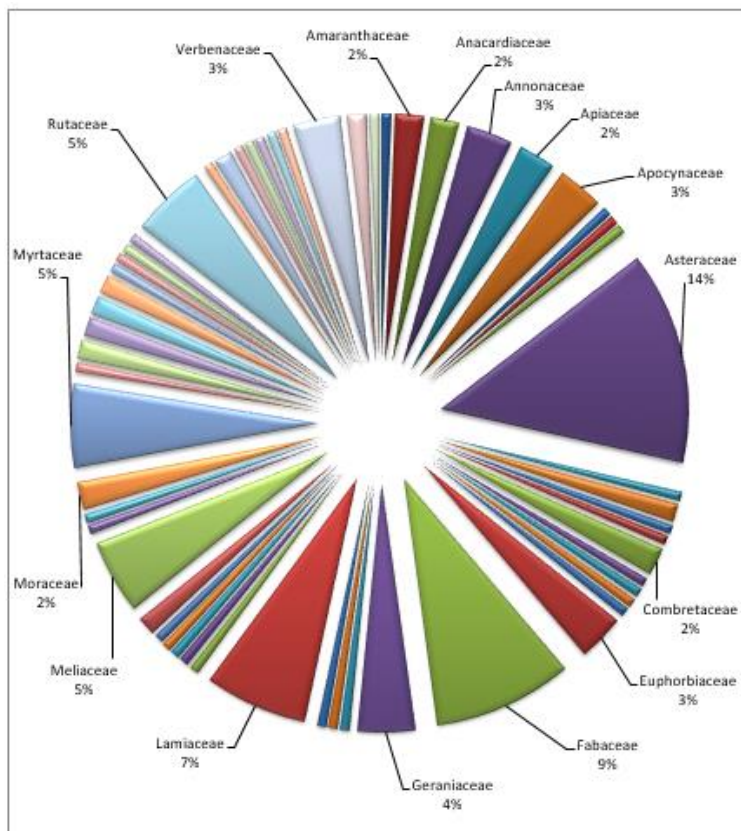


Fig 1: Pie chart representing the percentage of various families used against *H. contortus* from total plant reviewed (Less than 1% is not display)

Table 1: Anthelmintics activities shown by various medicinal plant extract on *Haemonchus contortus* by several researchers

Table 2: Anthelmintic activity shown by Essential oil obtained from different part of plant on *Haemonchus contortus* by several researcher

Plant species	Family	Tested product	Lethal concentrations/ biological activity	References
<i>Ocimum gratissimum</i>	Labideae	Essential oil	100% Mean egg hatch inhibition at 1.0% essential oil was diluted in aqueous solution of Tween 20	Pessoa <i>et al.</i> 2002
<i>Croton zehntneri</i>	Euphorbiaceae	Essential oil	EC ₅₀ value was 0.55 mg/ml for egg hatch assay and 1.17 mg/ml for larval development test	Camurçã-Vasconcelos <i>et al.</i> 2007
<i>Lippia sidoides</i>	Verbenaceae	Anethole (major constituents of essential oil)	EC ₅₀ value was 0.69 mg/ml for egg hatch assay and 2.11 mg/ml for larval development test	
		Essential oil		
		Thymol (major constituents of essential oil)	EC ₅₀ value was 0.40 mg/ml for egg hatch assay and 2.97 mg/ml for larval development test	

<i>Eucalyptus staigeriana</i>	Myrtaceae	Essential oil	EC ₅₀ value was 0.55 mg/ml for egg hatch assay and 2.49 mg/ml for larval development test	Macedo <i>et al.</i> 2010
	Gramineae	Essential oil		Katiki <i>et al.</i> 2011
<i>Cymbopogon schoenanthus</i>	Gramineae	Essential oil	EC ₅₀ in the egg hatch test was 0.324 mg/ml and 1.702 mg/ml for larval development test	
<i>Cymbopogon martini</i>	Lamiaceae	Essential oil	LC ₅₀ for egg hatch test, larval development assay, larval feeding inhibition assay and larval exsheathment assay was 0.04, 0.06, 24.66 and 0.009 mg/ml	
<i>Mentha piperita</i>	Myrtaceae	Essential oil	LC ₅₀ for egg hatch test, larval development assay, larval feeding inhibition assay and larval exsheathment assay was 0.13, 0.15, 28.17 and 0.03 mg/ml	Macedo <i>et al.</i> 2011
<i>Eucalyptus citriodora</i>	Verbenaceae	Essential oil		Macedo <i>et al.</i> 2013
	Asteraceae	Essential oil	LC ₅₀ for egg hatch test, larval development assay, larval feeding inhibition assay and larval exsheathment assay was 0.06, 0.06, 61.93 and 0.07 mg/ml	
<i>Lantana camara</i>	Zingiberaceae	Essential oil		
<i>Tagetes minuta</i>	Umbellifera	Essential oil	EC ₅₀ for larval development and inhibition of egg hatching was 2.71 and 1.14 mg/ml	
<i>Alpinia zerumbet</i>	Myrtaceae	Essential oil	EC ₅₀ value larval development test was 6.32 mg/ml	Ribeiro <i>et al.</i> 2013
<i>Coriandrum sativum</i>		Chitosan-encapsulated Essential oil		
<i>Eucalyptus staigeriana</i>	Asteraceae	Essential oil	EC ₅₀ value for egg hatch assay and larval development test was 0.53 and 1.67 mg/ml	Zhu <i>et al.</i> 2013a
	Asteraceae	Essential oil	EC ₅₀ value for egg hatch assay and larval development test was 0.94 and 3.88 mg/ml	
<i>Arisaema franchetianum</i>		Carvacrol (major constituents of both essential oil)	EC ₅₀ value for egg hatch assay and larval development test was 0.63 and 2.89 mg/ml	
<i>Arisaema lobatum</i>	Asteraceae	Essential oil	EC ₅₀ value for egg hatch assay and larval development test was 0.24 and 3.24 mg/ml	Zhu <i>et al.</i> 2013b
		1,8-cineole (major constituents of essential oil)		
<i>Artemisia lancea</i>		Camphor (major constituents of essential oil)	EC ₅₀ value for egg hatch assay and for larval development test was 1.63 mg/ml and 1.10 mg/ml. 74.1% inhibition of larval migration 10 mg/ml in larval migration inhibition assay	

<i>Eucalyptus citriodora</i>	Myrtaceae	Essential oil nanoencapsulated Essential oil	EC ₅₀ value for egg hatch assay and for larval development test was 0.48 mg/ml and 0.73 mg/ml. 95.6% inhibition of larval migration 10 mg/ml in larval migration inhibition assay	Ribeiro <i>et al.</i> 2014
	Myrtaceae	Essential oil Nanoemulsions	EC ₅₀ value for egg hatch assay and for larval development test was less than 0.32 mg/ml and 0.51 mg/ml. 97 % inhibition of larval migration 10 mg/ml in larval migration inhibition assay	Ribeiro <i>et al.</i> 2015
<i>Eucalyptus staigeriana</i>	Rutaceae	Essential oil	LC ₅₀ value for egg hatch assay and for larval development test was 1.82 mg/ml and 1.66 mg/ml. 77% inhibition of larval migration at 10 mg/ml in larval migration inhibition assay	Gáinza <i>et al.</i> 2015
<i>Citrus sinensis</i>	Myrtaceae	Essential oil	LC ₅₀ value for egg hatch assay and for larval development test was 4.64 mg/ml and 5.07 mg/ml. 60.3% inhibition of larval migration 10 mg/ml in larval migration inhibition assay	Macedo <i>et al.</i> 2015
	Poaceae	Citral (major constituents of essential oil)		
<i>Melaleuca quinquenervia</i>		Aqueous Decoction	LC ₅₀ value for larval development test was 7.80 mg/ml. 18.1% inhibition of larval migration 10 mg/ml in larval migration inhibition assay	
<i>Cymbopogon citratus</i>	Rutaceae	Essential oil	EC ₅₀ value for egg hatch assay and larval development test was 1.3 and 1.7 mg/ml	Qi <i>et al.</i> 2015
		Borneol (major constituents of essential oil) β-elemene (major constituents of essential oil) Essential oil	EC ₅₀ value for egg hatch assay and larval development test was 0.4 and 1.7 mg/ml	
	Myrtaceae	Essential oil	EC ₅₀ value for egg hatch assay and larval development test was 0.7 and 2.3 mg/ml	Grando <i>et al.</i> 2016
		Nanostructured Essential oil	EC ₅₀ value for egg hatch assay and larval development test was 0.2 and 1.8 mg/ml	
<i>Zanthoxylum simulans</i>	Lamiaceae	Essential oil	IC ₅₀ and IC ₉₀ value for egg hatch assay was 0.27 and 0.99 mg/ml and for larval development test was 0.97 and 2.32 mg/ml	Castilho <i>et al.</i> 2017
		Essential oil	IC ₅₀ and IC ₉₀ value for egg hatch assay was 1.52 and 5.63 mg/ml and for larval development test was 0.44 and 0.94 mg/ml	
<i>Melaleuca alternifolia</i>	Rutaceae	Essential oil	EC ₅₀ value for egg hatch assay and larval development test was 0.14 and 1.92 mg/ml	Ferreira <i>et al.</i> 2018
	Asteraceae	Essential oil		
	Lamiaceae	Essential oil	EC ₅₀ value for egg hatch assay and larval development test was 0.13 and 1.37 mg/ml	

<i>Hesperozygis myrtoidea</i>	Poaceae	Chitosan encapsulated nanoemulsion Essential oil	EC ₅₀ value for egg hatch assay and larval development test was 0.46 and 5.04 mg/ml	Macedo <i>et al.</i> 2019
<i>Citrus aurantifolia</i> (Fruit peel)	Apiaceae	Essential oil	LC ₅₀ value for egg hatch assay and for larval development test was 3.98 mg/ml and 4.02 mg/ml.	Castro <i>et al.</i> 2019
<i>Anthemis nobile</i> (Flower)	Lamiaceae	Essential oil	LC ₅₀ value for egg hatch assay and for larval development test was 1.50 mg/ml and 1.99 mg/ml.	Abidi <i>et al.</i> , 2020
<i>Lavandula officinalis</i> (Flower)	Lamiaceae	Essential oil	LC ₅₀ value for larval development test was 32.17 mg/ml.	Aouadi <i>et al.</i> , 2021
<i>Cymbopogon citratus</i>	Monimiaceae	Citral Methyl chavicol	LC ₅₀ and LC ₉₀ value for eggs hatching inhibition was 0.43 and 1.75 mg/ml. LC ₅₀ value was 10.68 mg/ml for Larval migration inhibition test	Silva-Aguayo <i>et al.</i> , 2021
	Lamiaceae	Eugenol Linalool	LC ₅₀ and LC ₉₀ value for eggs hatching inhibition was 1.81 and 6.29 mg/ml. LC ₅₀ value was 12.64 mg/ml for Larval migration inhibition test	Sousa <i>et al.</i> , 2021
<i>Anethum graveolens</i>		Eugenol (11%) + linalool (64 %)	LC ₅₀ and LC ₉₀ for egg hatch test was 0.249 and 0.797 mg/ml and 0.072 and 0.167 mg/ml for larval development test	
<i>Origanum majorana</i>		Methyl chavicol (27%) + linalool (57%)	IC ₅₀ for egg hatch test was 0.694mg/ml and LC ₅₀ value for larval development test was 0.044mg/ml.	
		Citral (49%) + linalool (38%)		
<i>Rosmarinus officinalis</i>	Rutaceae	Essential oil	IC ₅₀ for egg hatch test was 0.316mg/ml and LC ₅₀ value for larval development test was 0.117 mg/ml.	Garbin <i>et al.</i> , 2021
<i>Peumus boldus</i>	Rutaceae	Essential oil	IC ₅₀ for egg hatch test was 0.842 mg/ml and LC ₅₀ value for larval development test was 0.280 mg/ml.	Sebai <i>et al.</i> , 2022 (a)
	Lauraceae	Essential oil		
<i>Ocimum basilicum</i>	Meliaceae	Essential oil (Leaf)	EC ₅₀ value for egg hatch assay was 0.15 mg/ml.	Batool <i>et al.</i> , 2022
		Essential oil (seeds)		
		Essential oil (Leaf)	EC ₅₀ value for egg hatch assay was 0.16 mg/ml.	
	Meliaceae	Essential oil (seeds)	IC ₅₀ for egg hatch test was 0.006 mg/ml and IC ₅₀ value for larval development test was 2.536 mg/ml. IC ₅₀ value for larval migration was 3.963 mg/ml.	
<i>Citrus bergamia</i>	Cupressaceae	Essential oil	IC ₅₀ for egg hatch test was 3.206 mg/ml and LC ₅₀ value for adult worm motility was 0.5 mg/ml after 8h of exposure.	Meriema <i>et al.</i> , 2022
		Essential oil		

<i>Citrus X paradisi</i>	Asteraceae		EC ₅₀ value for Anthelmintic activity bioassays on ensheathed <i>H. contortus</i> L3 larvae was 1.63, 1.20 and 0.99 mg/ml after for 24, 48 and 72h of exposure.	Fantatto et al., 2022
<i>Laurus nobilis</i>	Myrtaceae	Essential oil (Carvone 70%)	IC ₅₀ for egg hatch test was 0.30 mg/ml.	Sebai <i>et al.</i> , 2022 (b)
<i>Azadirachta indica</i>	Verbenaceae	Essential oil (Citral chemotype)	IC ₅₀ for egg hatch test was 0.66 mg/ml.	Barbosa <i>et al.</i> , 2023
		Essential oil	IC ₅₀ for egg hatch test was 1.39 mg/ml.	
<i>Melia (M.) azedarach</i>	Verbenaceae		IC ₅₀ for egg hatch test was 1.75 mg/ml. IC ₅₀ for egg hatch test was 0.44 mg/ml. IC ₅₀ for egg hatch test was 0.65 mg/ml.	Ureña <i>et al.</i> , 2023
<i>Juniperus phoenicea</i>			IC ₅₀ for egg hatch test was 0.69 mg/ml.	
<i>Achyrocline satureioides</i>			IC ₅₀ for Exsheathed third stage larvae (L3) Test was 8.7 µg/ml after 72h of exposure	
<i>Myrtus communis</i>			IC ₅₀ for Exsheathed third stage larvae (L3) Test was 13.88 µg/ml after 72h of exposure	
<i>Lippia alba</i>			IC ₅₀ for egg hatch test was 1.72 mg/ml and LC ₅₀ value for adult worm motility was 3.45 mg/ml after 8h of exposure. IC ₅₀ for egg hatch test was 0.662 µg/L and LC ₅₀ value for adult worm motility was 0.036 µg/L after 8h of exposure	
<i>Lippia dominguensis</i> <i>Moldenke</i>			IC ₅₀ for egg hatch test was 0.456 µg/L and LC ₅₀ value for adult worm motility was 0.585 µg/L after 8h of exposure IC ₅₀ for egg hatch test was 0.352 µg/L and LC ₅₀ value for adult worm motility was 0.36µg/L after 8h of exposure IC ₅₀ for egg hatch test was 0.370 µg/L and LC ₅₀ value for adult worm motility was 0.305µg/L after 8h of exposure	
			IC ₅₀ for egg hatch test was 0.35 mg/ml and Adult worms motility assay induced 76.18% Mortality by highest concentration (1.00 mg/ml) after 8h of exposure. IC ₅₀ for egg hatch test was 10.42 mg/ml and LC ₅₀ value for Larval development test was 0.42 mg/ml	

			<p>IC₅₀ for egg hatch test was 0.7 mg/ml and 95.83 % immobility of adult worm's at 2.00 mg/ml after 8h of exposure.</p> <p>IC₅₀ for egg hatch test was 0.2 mg/ml and 100% Mortality at 2.00 mg/ml after 12h of exposure.</p> <p>IC₅₀ for egg hatch test was 0.3 mg/ml and 100% Mortality at 2.00 mg/ml after 12h of exposure.</p> <p>IC₅₀ for egg hatch test was 0.523 mg/ml and 95.8% Mortality at 1.00 mg/ml after 12h of exposure.</p>	
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Mode of action of plant metabolite on target organism

Rattan's extensive review highlights that plant metabolites have specific effects on the physiological functions of targeted species. These metabolites can impact the physiology of organisms through several mechanisms, such as interacting with vital enzymes, interfering with cellular signaling, disrupting neurotransmitter synthesis, and affecting metabolic pathways (Rattan, 2010). Medicinal plant species produce various secondary metabolites that can act as deterrents to insects and herbivores. Compared to single compounds, these metabolites often have longer-lasting effects. They provide a complex and multifaceted defense mechanism against pests and herbivores. For example, essential oils primarily affect the cholinergic system by inhibiting the activity of acetylcholinesterase. . When plant metabolites inhibit the activity of acetylcholinesterase (AChE), it results in the accumulation of acetylcholine, a neurotransmitter, in the synaptic cleft. This accumulation disrupts the normal neuromuscular transmission in the *Haemonchus contortus* (Kaur and Sood, 1982). As a consequence, the musculature of the parasite experiences paralysis or discoordination. The interruption of neuromuscular transmission has significant implications for the parasite's survival. The paralysis affects crucial functions, including food swallowing and movement through the digestive system. Consequently, the parasites are unable to feed and digest nutrients properly, leading to a state of starvation and energy deprivation. Without a functional digestive system and the inability to obtain nourishment, the parasites are unable to sustain themselves inside the host organism. This inhibition of AChE by plant metabolites ultimately disrupts the parasites' ability to survive and reproduce effectively.

Essential oils derived from *Ocimum basilicum* (basil) have been found to contain eugenol as one of their active constituents (Sousa *et al.*, 2021). Eugenol is a phenolic compound with various biological activities, including potential effects on cell morphology and division. Studies have reported that eugenol can cause alterations in cell shape and the formation of membrane blebs (Machado *et al.*, 2011). Membrane blebs are small protrusions or bulges that form on the cell membrane, often indicating cellular stress or damage. Additionally, eugenol has been shown to restrict cell growth and induce changes such as swelling and collapsing of the cell membrane (Table 2) (Ueda-Nakamura *et al.*, 2006). These effects on the cell membrane can disrupt its integrity and functionality. Moreover, eugenol has been found to arrest cell division, preventing the normal progression of the cell cycle (Ueda-Nakamura *et al.*, 2006). This disruption of cell division processes can hinder the proliferation and growth of cells. These reported effects of eugenol on cell morphology, membrane integrity, cell growth, and cell division highlight its potential impact on cellular processes. However, it's important to note that the specific effects of eugenol can vary depending on the concentration, exposure duration, and cell type studied. Katiki *et al.* (2011) observed significant anthelmintic activity in the essential oils obtained from *Cymbopogon schoenanthus*, *Cymbopogon martini*, and *Mentha piperita* against *H. contortus*. The precise mechanisms underlying this activity may involve disruption of the nematode's nervous system, inhibition of essential metabolic processes, or damage to cellular structures, leading to paralysis or death of the parasite.

The phytochemical profile of *Cocos nucifera L.* (coconut) has been studied, revealing the presence of various bioactive compounds such as alkaloids, flavonoids, phenols, triterpenes, and condensed tannins (Oliveira *et al.* 2009). Condensed tannins found in coconut have shown antiparasitic activities (Costa *et al.*, 2010). Condensed

tannins are polyphenolic compounds that have the ability to bind to proteins. In the context of parasites, condensed tannins can bind to proteins present in the cuticle (outer protective layer), oral cavity, esophagus, and cloaca, leading to chemical and physical damage in the parasite. By interacting with proteins in these specific areas, condensed tannins can disrupt the normal functions of the parasite's cuticle and various organs, impairing their ability to survive and reproduce. This antiparasitic activity of condensed tannins contributes to their potential use in combating parasitic infections.

Scientific research has revealed several intriguing properties of artemisinin, a potent active ingredient found in essential oils and plant extracts derived from various species (*A. vestita*, *A. lancea*, *A. maritime* and other) of *Artemisia* (Zhu *et al.* 2013; Akkari *et al.* 2014 Irum *et al.* 2015). Jia *et al.* (2016) observed that artemisinin disrupts mitochondrial membrane potential and induces the release of cytochrome c into the cytoplasm. Furthermore, artemisinin exerts inhibitory effects on the electron transfer and oxidative phosphorylation processes within mitochondria, which are crucial for cellular energy production. These actions ultimately lead to the activation of caspase-3-mediated apoptosis, a vital pathway involved in programmed cell death (Li *et al.*, 2005).

Essential oils contain a variety of lipophilic compounds, such as terpenes and phenolic compounds, which can integrate into the lipid bilayer of cell membranes. According to Bakkali *et al.* (2008), these compounds interact with the chemical structures of lipids, polysaccharides, and phospholipids, causing significant alterations in membrane integrity. The incorporation of essential oil components into the lipid bilayer disrupts the orderly arrangement of the membrane. This disruption increases membrane permeability, allowing the uncontrolled flow of ions and other molecules into and out of the cell. The result is a loss of essential cellular homeostasis, leading to cell dysfunction and, ultimately, cell death. The disruption of the lipid bilayer also leads to membrane depolarization. The normal function of a cell membrane involves maintaining a specific membrane potential, essential for processes such as nutrient transport and signal transduction. When essential oils cause depolarization, this potential is disrupted, impairing the cell's ability to function properly. This mechanism is particularly effective against microbial cells, which rely on membrane potential for energy production and metabolic processes. Octopamine is a critical neurotransmitter in invertebrates, analogous to norepinephrine in vertebrates. It plays a vital role in modulating physiological functions, including heart rate, behavior, and metabolism. Octopamine receptors are G-protein coupled receptors that, when activated by octopamine, trigger a cascade of intracellular events. Essential oils can interfere with the normal functioning of octopamine receptors. By binding to these receptors or altering their conformation, essential oils disrupt the signaling pathways mediated by octopamine. This interference can lead to a range of physiological effects, from impaired locomotion and feeding behavior to altered reproductive functions. The impact on octopamine receptors extends to neuromodulation and neurohormonal regulation. Essential oils can alter the release and reception of neurotransmitters, affecting neural communication and hormonal balance. This disruption can incapacitate pests by affecting their nervous system and overall physiology (Rattan, 2010). The ability of essential oils to target multiple cellular and physiological pathways makes them effective against a wide range of pests and pathogens. This broad-spectrum efficacy is advantageous for integrated pest management, where essential oils can be used to control various insects and microorganisms without relying on synthetic chemicals. The complex and multifaceted mechanisms of essential oils reduce the likelihood of resistance development. Unlike synthetic pesticides that often target a single site of action, the multiple targets of essential oils make it more difficult for pests and pathogens to develop resistance. This property makes essential oils sustainable options for long-term use in pest and microbial control strategies.

Azadirachtin, an active ingredient found in *Azadirachta indica* (Neem), disrupts hormonal balance in targeted species. is an effective bioactive compound known for its role in disrupting hormonal balance in various insect species (Batool *et al.*, 2022). It interferes with the endocrine system, particularly the molting process, by mimicking the hormone ecdysone, which is crucial for insect growth and development. This disruption prevents insects from progressing through their life stages, ultimately leading to their death. Azadirachtin also acts as an antifeedant, reducing the feeding activity of insects, and inhibits oviposition, further reducing insect populations. Its broad spectrum of activity makes it an important component in integrated pest management strategies, offering an eco-friendly alternative to synthetic pesticides. Pyrethrin, derived from *Chrysanthemum* species, specifically *Chrysanthemum cinerariifolium*, operates through a different mechanism. It targets the mitochondrial system of insects, disrupting the normal exchange of sodium and potassium ions across nerve cell membranes. Pyrethrins bind to sodium channels in the nerve cells, keeping them open longer than usual. This prolonged opening leads to an influx of sodium ions and a subsequent disruption in nerve impulse transmission, resulting in paralysis and death of the insect. Pyrethrins are valued for their rapid knockdown effect on a wide range of insect pests and are commonly

used in household insecticides, veterinary applications, and agricultural pest control. Secondary metabolites produced by medicinal plants exert their effects on targeted organisms through various physiological pathways. Azadirachtin's hormonal disruption and pyrethrin's neurotoxic effects exemplify how plant-derived compounds can be harnessed for effective pest control while minimizing environmental impact and the development of resistance seen with many synthetic pesticides. These metabolites provide a comprehensive defense strategy against pests and herbivores, impacting crucial systems like the cholinergic, octopaminergic, hormonal, and mitochondrial systems. (Rattan, 2010).

Future Scope and Conclusion

In recent years, the effectiveness of traditional pasture management techniques and the extensive use of chemical anthelmintics in controlling *Haemonchus contortus*, has been limited due to the development of drug resistance. As a result, researchers worldwide have turned their attention to exploring alternative approaches utilizing plant metabolites as anthelmintics. Several plants have been identified for their potential anthelmintic properties, showing promising effects against *H. contortus* (Table 1 and Table 2). Understanding the specific mechanisms by which these plant extracts and essential oils exert their anthelmintic effects can aid in developing more targeted treatments and potentially identifying new anthelmintic compounds. These plant-based anthelmintics can be integrated into existing parasite control programs, either alone or in combination with synthetic drugs, to enhance efficacy and reduce resistance development. These plant extracts essential oils provide natural alternatives to synthetic anthelmintics, which can be particularly useful in organic farming systems and for reducing the development of drug-resistant parasites. Plant-based anthelmintics are typically more environmentally friendly than synthetic chemicals, reducing the risk of environmental contamination and promoting sustainable agricultural practices. These plant extracts can be used alongside existing anthelmintic drugs to enhance overall efficacy and help manage resistance. For instance, they can be integrated into rotational deworming programs to reduce the selection pressure for resistant nematode strains. Incorporating natural anthelmintics into a broader integrated pest management (IPM) approach, which includes rotational grazing, selective breeding for resistance, and proper pasture management, can provide a more comprehensive solution to parasite control. Further research is necessary to elucidate the specific bioactive compounds responsible for the anthelmintic activity, optimize extraction methods, and assess safety profiles in livestock.

However, to enhance the efficacy of these plant-derived drugs, recent technologies have been incorporated, with nanotechnology garnering significant interest among researchers due to its unique properties. Nanoformulations, such as nanoparticles, nanoemulsions, and nanoencapsulation, have been widely employed in the medical field owing to their small size and larger surface area, which exhibit antibacterial, antimicrobial, and antifungal properties.

Notably, some studies have investigated the anthelmintic potential of nanotechnology against *H. contortus*. For instance, Tomar *et al.* 2017, embarked on an innovative study where they synthesized silver nanoparticles utilizing an extract from *Azadirachta indica*. As we have earlier discussed Neem is renowned for its medicinal properties, including anti-inflammatory, antimicrobial, and antiparasitic effects. The synthesis of silver nanoparticles involved a green chemistry approach, reducing the environmental impact compared to conventional chemical synthesis methods. The researchers conducted a series of bioassays to evaluate the anthelmintic potential of these nanoparticles, finding that they effectively inhibited the motility and survival of *H. contortus* larvae. Similarly, in 2017, Preet and colleagues synthesized silver nanoparticles using an extract from the *Ziziphus jujube* plant, which is traditionally used in various cultures for its medicinal properties, such as anti-inflammatory, antioxidant, and antimicrobial activities. The researchers then assessed the anthelmintic potential of these nanoparticles through Egg Hatch Assay and Adult Mortality Assay experiments. They evaluated the nanoparticles' effects on the mortality, motility, and morphology of *H. contortus*. Additionally, they studied the biochemical changes induced in the parasite, such as alterations in nutritional outputs, to understand the mechanism of action of these nanoparticles. In a Ribeiro *et al.* 2014 study, they developed nanoemulsions using essential oils from *Eucalyptus citriodora*, a plant known for its strong antimicrobial and anti-inflammatory properties due to its high citronellal content. Nanoemulsions are submicron-sized emulsions that enhance the solubility, stability, and bioavailability of hydrophobic compounds like essential oils. The researchers formulated these nanoemulsions and tested their anthelmintic activity against *H. contortus*. They observed significant reductions in larval motility and adult worm viability, suggesting that the nanoemulsions effectively delivered the active compounds to the parasite, potentially disrupting its biological functions and leading to its death. In a subsequent study in 2015, Ribeiro and his team

focused on synthesizing nanoemulsions with essential oil from *Eucalyptus staigeriana*, which contains bioactive compounds such as limonene and citral known for their antimicrobial and antiparasitic properties. They employed both in vitro assays, which involved exposing *H. contortus* larvae and adults to the nanoemulsions, and in vivo tests on infected livestock. The results showed that the nanoemulsions significantly impaired the parasites' ability to survive and reproduce, demonstrating a promising new approach for controlling parasitic infections in livestock. These research emphasized the potential of combining essential oils and nanotechnology to develop more effective and environmentally friendly anthelmintic treatments.

The extensive research conducted on plant-derived phytochemicals and essential oils provides compelling evidence for their potential as effective anthelmintics. With the growing threat of drug-resistant parasites, exploring alternative treatments becomes imperative. Harnessing the power of plants not only offers a sustainable approach but also provides an opportunity to discover novel therapeutic agents. Further investigations and optimization of these natural compounds may lead to the development of safe, cost-effective, and environmentally friendly anthelmintic strategies that can combat drug resistance and improve global health. The use of nanotechnology has shown promise in enhancing the potential of plant extracts and essential oils as anthelmintics. However, further research is needed to explore the synergistic approach of combining chemical anthelmintics with these nanoformulations to further enhance their efficacy.

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Conflict of Interests

There is no conflict of interest.

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