Animal Health

Review

Azadirachta indica Leaf Extracts to Control Gastrointestinal Nematodes in Sheep

Nelson Correa Herrera *, Josmel Salas Romero **, Janet Quiñones-Galvez ***

*Faculty of Agricultural Sciences. The Maximo Gomez Baez University of Ciego de Avila, Carretera a Morón, km 9,5, Ciego de Ávila, Cuba.

**Faculty of Agricultural Sciences. The Ignacio Agramonte y Loynaz University of Camaguey, Cuba

***Bioplants Center, The Maximo Gomez Baez University of Ciego de Avila, Carretera a Morón, km 9,5, Ciego de Ávila, Cuba.

Correspondence: nelsonch9610@gmail.com

Received: June 2023; Accepted: August 2023; Published: September 2023.

ABSTRACT

Background: Nematodes are gastrointestinal parasites that infect ovine. They can cause economic losses leading to the most serious problems in extensive ovine production, particularly in tropical areas, of up to a billion dollars worldwide. **Aim.** To collect information about the main biological activities of *A. indica* (*Azadirachta indica* A. Juss) tree leaf extracts to evaluate their possible use in the future as a clinical treatment to control gastrointestinal nematodes in sheep. **Development:** The productive and economic problems caused by gastrointestinal parasitosis in animals, where anthelmintic resistance results from failure to use anthelmintics at adequate levels for proper livestock productive potential. Hence, alternative methods to control gastrointestinal nematodes capable of reducing the parasitic burdens are being studied presently. The attribute of alternative methods is to reduce the dependence on commercial anthelmintics, which means fewer treatments to animals a year, thus permitting the preservation of susceptible parasites on the farm. The utilization of farms with anthelmintic properties has become one of the most interesting alternatives recently. The *A. indica* tree is one of the plants that has antiparasitic activity. **Conclusions:** *A. indica* (*Azadirachta indica* A. Juss) tree leaf extracts constitute an alternative ecological source to control gastrointestinal nematodes in sheep, due to their anthelmintic effect and the promotion of biodiversity. Compared to chemical anthelmintics, they have a lower chance of developing resistance, demonstrating safety, cost-effectiveness, and ease of use, since they are present in the environment, and are useful to farmers. The plant extracts might integrate into a program for a comprehensive control method designed to control parasites

Como citar (APA)
Correa Herrera, N., Salas Romero, J., Quiñones-Galvez, J. (2023). *Azadirachta indica* Leaf Extracts to Control Gastrointestinal Nematodes in Sheep. *Journal of Animal Prod.*, *35*(2), https://revistas.reduc.edu.cu/index.php/rpa/article/view/e4533

sustainably in ovine production systems. They could also be part of studies on phylum plathelminth parasites, with a broader epidemiological prevalence.
Keywords: *Azadirachta*, plant extracts, sheep, *Trichostrongyloidea* (*Source*: *MeSH)*

INTRODUCTION

Parasitic diseases, particularly gastrointestinal nematodes (GIN) are among the most commonly generated elements in sheep around the world, causing the main financial losses resulting from feed cuts, stunted development, a reduction in draining, weight loss, disabled maturity, and in cases of massive contamination, high mortality rates (Chinchilla *et al*., 2020). These parasites affect the health and animal welfare, reducing their productive potential critically, since GIN infections lead to higher mortality (Camacho *et al.*, 2021).

Effective and potentially non-dangerous measures to control endoparasites are indeed necessary to reduce the high economic losses by the farmers (Rafique *et al*., 2022).

Traditional medicinal plants used as alternative dewormers demonstrated significant results in both industrial and developing countries. Besides, medicinal plants have been used in many countries traditionally for years (Azam *et al*., 2019; Majeed *et al*., 2020; Hassan *et al*., 2020; Adoho *et al*., 2022).

Previous findings related to traditional medicinal plants proved that many plant species act as anti-parasitic drugs and are an alternative to anthelmintics (Abbas *et al*., 2020), and can be useful to lower the influx level of parasites in livestock (Sobhy *et al*., 2021); they are sustainable and ecologically acceptable (Rafique *et al*., 2022). Among the most commonly used species is Neem (*Azadirachta indica* A. Juss. *Meliaceae*) (Souza *et al*., 2016). The *Azadirachta indica* tree (Neem) is known for its medicinal properties and has been used to treat gastrointestinal nematodes and other infections in various parts of the world (Biswas *et al*., 2022).

However, Ragab *et al*. (2020) said that the products derived from many herbs and plants contain bioactive compounds and agents that can be used to treat diseases and are comparatively harmless. Almost 25% of the synthetic drugs are extracted from medicinal herbs and plants, as reported by FAO (Food and Agriculture Organization). In developing countries, almost 80% of the population depends on herbal medicine to treat different diseases.

Hence, developing and including anthelmintic plant extracts as part of comprehensive animal management is critical to improve animal welfare, and reduce the financial losses caused by nematodes. Accordingly, this paper aims to collect information about the main biological activities of *A. indica* (*Azadirachta indica* A. Juss) tree leaf extracts to evaluate their possible use in the future as a clinical treatment to control gastrointestinal nematodes in ovine.

DEVELOPMENT

Description of *Azadirachta indica*

It is a fast-growing tree (20-23 m high), with a straight trunk (4-5 feet) (Figure 1). The leaves are compound and imparipinnate, each having 5-15 folioles. The fruits are green drupes that turn golden yellow when ripening between June and August (Alzohairy, 2016)**.** The flowers are aromatic (Chaguthi *et al*., 2018), having a bisexual nature and pale yellow and white color (Quraishi *et al*., 2018).

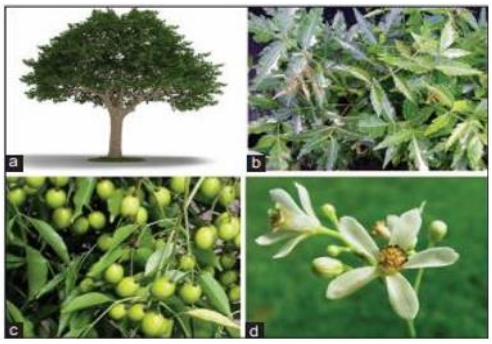

Figure 1. *Azadirachta indica* tree and its various parts a) Tree, b) Leaves, c) Fruits, d) Flowers (Rahmani *et al.*, 2018).

The taxonomic position of *Azadirachta indica* (Neem) is classified in Table 1 (Uzzaman, 2020).

Table 1. Taxonomy of *Azadirachta indica* (Uzzaman, 2020)

Kingdom	***Plantae***
Sub-kingdom	*Traqueobionta*
Division	*Magnoliophyta*
Class	*Eudicot*
Subclass	*Rosidae*
Order	*Sapindales*
Family	*Meliaceae*
Genus	*Azadirachta*
Species	*A. indica*

Origin and geographical distribution

Azadirachta indica is widely spread in all the Indian continent (Bendigeri *et al*., 2019). Neem is extensively cultivated in several Asian countries, such as India, Nepal, Thailand, Cambodia, Indonesia, Sri Lanka, Burma, Pakistan, Bangladesh, and Vietnam (Tinghui *et al*., 2001). A significant amount of Neem is also spread in African countries, such as Senegal, Guinea, Ghana, Mali, Mauritania, Nigeria, Ethiopia, Kenya, Sudan, Tanzania, Somalia, and Mozambique. It is

also widely spread in Central America and South America, namely Guyana, Tobago, Jamaica, Surinam, The Dominican Republic, Mexico, Bolivia, Brazil, and Saint Lucia (Tinghui *et al*., 2001). Oli and Gautam (2022) reported that the Neem tree population in Senegal comprises 18-30 million. However, more than 60% of the population of *A. indica* is located in India (Tinghui, 2001).

Chemical composition

The identification of different compounds and active agents of the plant generates different advances and contributions to using its potential. The compounds are isolated and identified, for instance, their group, effects on the agents applied, and the benefits for mankind in their race to obtain clean, non-contaminating products that protect the environment. Technological advances have enabled the isolation and obtaining of complex molecules aiming to manufacture biodegradable products that can control crop-attacking pests efficiently and effectively, and are capable of protecting human health using natural products without adverse effects. Hence, *A. indica* has become an important alternative for the optimization of its compounds, including applications in favor of human well-being (Chica, 2018).

The *A. indica* tree contains hundreds of compounds (phytochemicals), many of which have been found to be bioactive, and have a diverse usefulness by themselves. Of the more than 300 unique compounds identified in this tree, azadirachtin, gedunin, and nimbolide are some of the most abundant. All of them have been defined as potential medications having a broad range of biological actions (Saleem *et al*., 2018; Braga *et al*., 2020; Nagini *et al*., 2021). Two recent reviews made by Saleem *et al*. (2018) and Gupta *et al*. (2017) have studied the extensive phytochemistry of *A. indica* (Marina and Scott, 2022).

Medicinal properties

Extracts from this tree (*A. indica*) have been widely used as treatments to promote health since ancient times due to their wide variety of therapeutic properties (Rahmani *et al*., 2018). Several parts of the tree have been used for thousands of years in Indian traditional medicine due to their antipyretic, antacid, antiparasitic, antibacterial, antiviral, antidiabetic, contraceptive, anti-cancerous, antioxidant, anti-fungal, and dental properties, including other curative and protecting properties (Alzohairy, 2016; Marina and Scott, 2022) (Figure 2).

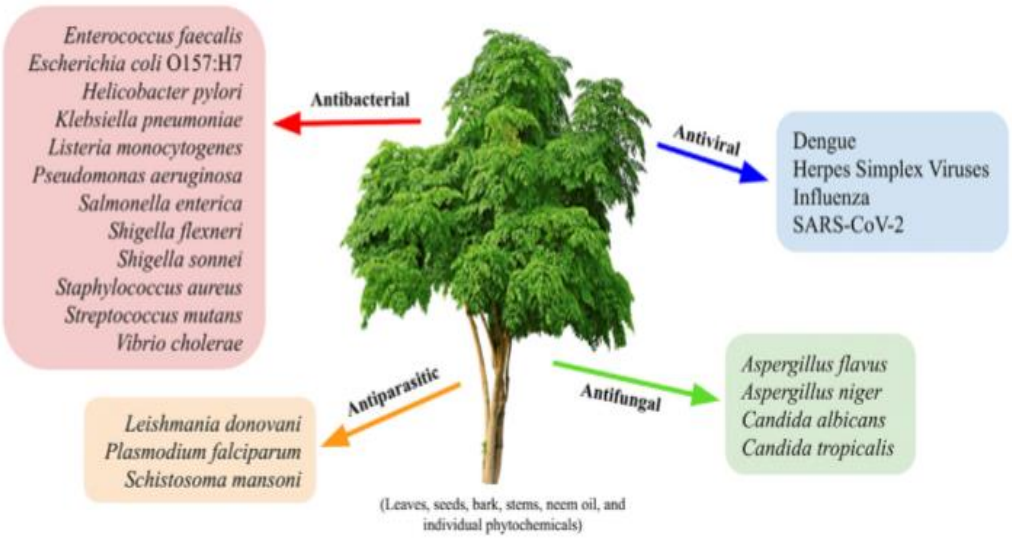

Figure 2. Main antimicrobial targets of *A. indica, Azadirachta indica*. Every part of *A. indica* (leaves, seeds, crust, and stems), the oil, and single phytochemicals associated with *A. indica* have proven antibacterial, antiviral, antiparasitic, and/or anti-fungal activities (Marina & Scott, 2022).

Gastrointestinal nematodes in sheep

Gastrointestinal nematodes (GIN) are cylindrical worms that inhabit the digestive tract of ruminants and are considered relevant parasites in livestock management, especially in intensive systems, in tropical and temperate climates (Craig, 2018). The adult parasites copulate, producing an enormous quantity of eggs, which are expelled in the feces where they grow until they become infecting larvae (L_3), contaminating the grass. The animals get infected through the ingestion of grass contaminated with these larvae (Reyes *et al*., 2022).

Ovine-affecting nematode species

Gastrointestinal nematodes in the *Trichostrongylidae* family are some of the most significant parasites living in small ruminants worldwide (Elseadawy *et al*., 2018). *Ostertagia* spp., *Haemonchus contortus*, *Trichostrongylus* spp., *Nematodirus* spp., and *Marshallagia marshalli* are the main GINs found in temperate sheep (Dey *et al*., 2020; Sharma *et al*., 2020).

Moreover, López *et al.* (2013) reported that in the tropical and subtropical regions, gastrointestinal parasites are one of the main agents affecting sheep health, coinciding with the previous reports. Some of these nematodes are *Haemonchus contortus* (the one with the highest prevalence in the world and one of the major causes of financial losses in sheep production), *Trichostrongylus colubriformis*, *Nematodirus*, *Oesophagostomum*, *Cooperia*, *Strongyloides*, *Teladorsagia*, *Chabertia*, *Bunostomum*, *Trichuris*, and *Dictyocaulus* (Cruz *et al.*, 2017).

Consequences of sheep production

Infection caused by gastrointestinal nematodes (GIN) is a challenge for small and large animals worldwide (Dey *et al*., 2020). Charlier *et al*. (2020) said that these parasites have a significant economic impact on industry through the effects on animal production and treatment costs.

However, when *Haemonchus* spp. is prevalent, it causes blood loss, accompanied by a sudden drop in hematocrit values, low feed conversion, difficulties in weight gain, loss of appetite, delayed growth, and even death. The young animals are especially susceptible to economic losses for farmers (Scott, 2017).

Moreover, gastrointestinal helminths also affect agricultural systems globally (Alzahrani *et al.*, 2016). These parasitic infections interrupt nutrient intake by animals, resulting in a lower weight and an increase in the animal's susceptibility to secondary infections (López *et al.*, 2020).

Existing control strategies

Due to the productive and economic problems caused by gastrointestinal parasitosis in animals, where anthelmintic resistance results from failure to use anthelmintics at adequate levels for proper livestock productive potential, alternative methods to control gastrointestinal nematodes capable of reducing the parasitic burdens are being studied presently (Aguilar *et al.*, 2013).

The attribute of alternative methods is to reduce the dependence on commercial anthelmintics, which means fewer treatments to animals a year, thus permitting the preservation of susceptible parasites on the farm. Likewise, they could be used by farmers who have found antiparasitic resistance problems. In the face of parasitosis, alternative control methods are emerging, such as the efficient use of antiparasitic treatments, grazing management, resistant breeds, and vaccines. Moreover, biological control based on fungi with nematophagous activity, copper needles, nutritional management, and selective antiparasitic treatments using FAMACHA. Also important is the inclusion of anthelmintic plants, as one of the most promising alternatives in recent years (Torres and Higuera, 2021).

Azadirachta indica leaf extracts to control gastrointestinal nematodes in sheep

Different studies have reported the antiparasitic effect of *A. indica* leaves (Cruz *et al.*, 2017), with variable results, which could be caused by the type of extract, the collecting method of the material used, and the phenological state of the plant, which might change the active compound's type and concentration (Moya and Escudero, 2015); Cruz *et al.* (2017), demonstrated a significant reduction of gastrointestinal nematodes in the excreta following the administration of 0.8 g/kg of aqueous extract of *A. indica leaves.*

Nevertheless, a study done by Sakti *et al*. (2018), on aqueous foliar infusion of *A. indica*, at 6% and 8% showed *in vitro* and *in vivo* anthelmintic activity against *H. contortus*, by reducing egg

hatching, the motility of adult worms, and egg feces counts per gram, after 6 weeks of treatment *in vivo*. The infusion of *A. indica* has a potential bio-anthelmintic activity against *H. contortus*.

Furthermore, a study done by Rafique *et al*. (2022), proved the efficacy of aqueous, methanolic, and ethanolic extracts of dry leaves of medicinal plants *Moringa oleifera* and *Azadirachta indica* for ovicide and larvicide activities against *Haemonchus*, *Trichuris*, *Coccidia*, and *Trichostrongylus* collected from wild sheep (*Ovis orientalis orientalis*). The general findings of this study demonstrate that the extracts of *Moringa oleifera* and *Azadirachta indica* leaves have a significant natural efficacy activity against sheep GINs, and could be a natural alternative to synthetic anthelmintics to treat worm infections in animals.

In another study conducted by Rehman *et al*. (2023), the authors evaluated the phytochemical composition, ovicide, and larvicide activity of the methanolic extracts and the ethyl acetate from *Azadirachta indica*. The results showed that these extracts had an effect on egg hatching and larval motility. The ethyl acetate showed the fastest lethal effect on adult worms using lower doses than the methanolic extract. Moreover, the methanolic extract was more effective than the ethyl acetate in the prevention of egg incubation. This paper demonstrates that the dissolvent used in the extraction affects the phytochemical composition and anthelmintic activity of *A. indica* largely, which is effective in controlling helminths.

Extract action mechanisms

The mode of action of bioactive compounds of *A. indica* has been identified, affecting in four different ways: they reduce the feeding capacity of parasites, regulate the parasite growth, sterilize and inhibit motor action by inhibiting the synthesis of chitin (Szwako *et al.*, 2017). The bioactive compounds of *A. indica* are easily degradable, and leave no toxic traces, since they do not accumulate in the food chain or the soil or other plants (Szwako *et al.*, 2017).

Extract pros and cons

The utilization of extracts has certain advantages over current veterinary treatments, including the availability, the lack of adverse effects, and easy access. The plant's extracts and beverages can be tried *in vitro* and *in vivo* thanks to their anthelmintic potential (Ahmed *et al*., 2023). They permit meat or milk consumption during the treatment, and can be used in a herd with the presence of resistance to normally used chemicals (Munguía *et al*., 2013). They are efficient against synthetic drug-resistant species, have little or no risk of developing resistance, and are friendly to the environment (Lalthanpuii and Lalchhandama, 2020). However, Castagna *et al*. (2020) referred to the lack of consistent *in vitro* and *in vivo* studies about the utilization of the plant as an anthelmintic, creating doubts about its validity and reliability. Other doubts include uncertainty about the efficacy of the plant, non-specific responses, non-reproducible preparations, and possible adverse effects (Ahmed *et al*., 2023).

Comparison with other control methods

Kumar *et al*. (2019), on the difference between the use of synthetic drugs and anthelmintic plants to control gastrointestinal parasites, said that synthetic anthelmintics are costly, whereas plant-based anthelmintics are not as expensive. These drugs cause problems related to drug residues while the ones from plants are drug-free. Additionally, there is a possibility for drug resistance following prolonged use of synthetic anthelmintics, while plant-based anthelmintics are less prone to create this resistance. Synthetic drugs are inexistent in rural areas, whereas plant-based anthelmintics are easily available and do not cause pollution; they are ecological and promote biodiversity.

Limitations and perspectives

One of the limitations of extracts use, according to Guerrero, (2018), is that the concentrations of bioactive substances used *in vitro* do not always correspond to the bioavailability of the living animal. Besides, some of the active compounds may have adverse effects, so it is necessary to validate the antiparasitic effects associated with their potential anti-nutritional effect, as well as other secondary effects. However, Kumar *et al*. (2019), considered the prolonged collection, preparation, and administration of ingredients. Moreover, in the future, the extracts must comply with the requisites for an ideal anthelmintic agent, as stated by Ahmed *et al*. (2023), who noted these extracts must have a broad spectrum of action, a high rate of treatment with a single dose, low toxicity to the host, and cost-effectiveness. Other perspectives refer to the need to establish and apply a framework regulation and standardization policy (Kumar *et al*., 2019), and encourage extract trading, considering that 80% of the population in developing countries depend on herbal medicine, creating excellent marketing possibilities (Kumar *et al*., 2019).

CONCLUSIONS

A. indica (*Azadirachta indica* A. Juss) tree leaf extracts constitute an alternative ecological source to control gastrointestinal nematodes in sheep, due to their anthelmintic effect and the promotion of biodiversity. Compared to chemical anthelmintics, they have a lower chance of developing resistance, demonstrating safety, cost-effectiveness, and ease of use, since they are present in the environment, and are useful to farmers. The plant extracts might integrate into a program for a comprehensive control method designed to control parasites sustainably in ovine production systems. They could also be part of studies on phylum plathelminth parasites, with a broader epidemiological prevalence.

ACKNOWLEDGMENTS

This result is part of a Local and International Project: FSPI Agrecocaribe: Utilization of Beneficial Native Microorganisms and Natural Products in Agricultural Systems. We thank everyone who participated in this result one way or another.

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AUTHOR CONTRIBUTION STATEMENT

Research conception and design: NCH, JSR, JQG; data analysis and interpretation: NCH, JSR, JQG; redaction of the manuscript: NCH, JSR, JQG.

CONFLICT OF INTEREST STATEMENT

The authors state there are no conflicts of interest whatsoever.