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Review Article

Botanicals: A Promising Control Strategy Against Highly Zoonotic Foodborne Trichinosis

Abdullah F. ALSAYEQH [1 (*)]

[1] Department of Veterinary Preventive Medicine, College of Veterinary Medicine, Qassim University, Buraidah, SAUDI ARABIA

(*) **Corresponding author:**
Abdullah F. ALSAYEQH
Phone: + 966 548434310
E-mail: a.alsayeqh@qu.edu.sa

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Abstract

Trichinosis is a highly zoonotic disease caused by *Trichinella spiralis* in humans. The disease is majorly transmitted through the consumption of raw or undercooked meat. About 10000 people get infected with *T. spiralis* every year. Signs and symptoms of the disease may vary from mild to severe infection, depending on the worm load. Albendazole and mebendazole are two main anthelmintics that have been in use to treat trichinosis for a long time. Albendazole is a very effective drug in the early stages of the *T. spiralis* infection, but resistance has been reported multiple times. Drug resistance is the most prevailing issue that needs to be addressed as early as possible. Scientists have focused on the development of novel drugs for the treatment of *T. spiralis* infection. Botanical compounds have multiple medicinal and therapeutic properties which make them able to treat multiple parasitic diseases. Botanical compounds are considered the best alternatives for the development of new drugs for the treatment and control of trichinosis. This review covers the detailed mechanism of action of multiple botanical compounds for a better understanding of the formulation of new drugs. Saponins, tannins, and phenolic acids have potent anthelminthic activity against trichinosis.

Keywords: Botanical compounds, Food borne, Food safety, Meat, Mechanisms, Trichinosis, *T. spiralis*, Zoonosis

Introduction

Trichinosis, also known as Tricinellosis, is a parasitic disease that spreads through the consumption of undercooked contaminated meat [1]. Pork meat is the major source of the transmission of the disease while other carnivores also spread the disease to humans [2]. Trichinosis is among the 10 most common food-borne zoonotic diseases of humans [3]. Trichinosis can also be caused by the consumption of beef meat when it becomes contaminated with a pathogenic agent [4]. The etiological agents of trichinosis are multiple *Trichinella* spp., among all *Trichinella spiralis* is the most common cause of the infection [5]. *T. spiralis* is the smallest known nematode (2nd largest phylum in the animal kingdom) which belongs to the family Trichinellidae [6]. The average size of male nematodes is 1.4-1.6 mm while females are relatively larger up to 1.4-4 mm [7]. *T. spiralis* is a ubiquitous roundworm that infects about ten thousand people annually around the globe [8]. The infection rate is higher in the countries where swine (pork) meat is consumed commonly [9]. The mortality rate of people infected with trichinosis is quite low (about 0.2%) globally [10]. The fatality ratio may increase when the infection becomes severe and untreated [11]. However, the signs and symptoms of the disease may vary from mild to severe [4]. The signs and symptoms of the infection depend on the phase of the infection [12]. There are 2 phases of the infection: enteral (affecting the intestine of the patient) and parenteral (affecting the organs and parts outside of the intestine) [13]. During the initial stage of the infection, *T. spiralis* invades the intestine of the patient and causes mild to severe symptoms including vomiting, abdominal pain, dyspepsia, heartburn, and diarrhea [14-16]. These signs and symptoms usually vary with the worm load, small burdens cause mild or no signs and symptoms of the disease while large worm burdens cause severe expression of the infection [17]. When *T. spiralis* migrates from the intestine to the other parts of the body, the severity of the infection increases [18,19]. Periorbital edema, vasculitis, muscle pain, fever, weakness, and splinter hemorrhage in nails are some common signs and symptoms in the case of the parenteral phase of the infection [12,20]. To cure the disease, multiple anthelmintics have been in use for a long time [21].

Albendazole and mebendazole are two main anthelmintics that have been in use to treat trichinosis for a long time [22].

Both drugs are the first line of treatment for trichinosis and are effective in the early stage of the infection [23,24]. However, some other drugs including flubendazole and benzimidazole-2-carbonate derivatives can also be used to treat human trichinosis [25,26]. Albendazole and mebendazole expel *T. spiralis* from the intestinal tract of the infected patient by disrupting the formation of microtubules [27]. They bind with the colchicine site of β-tubulin which results in the inhibition of the polymerization of the microtubule and cell division [28]. Disruption in the microtubule formation directly affects glucose absorption [29]. The mobility of *T. spiralis* is retarded due to the absence of an adequate glucose level to move in the body [30]. This will ultimately kill the parasite and flush it out of the intestine of the body *(Fig. 1)*. However, resistance against antiparasitic drugs is a major problem to be solved.

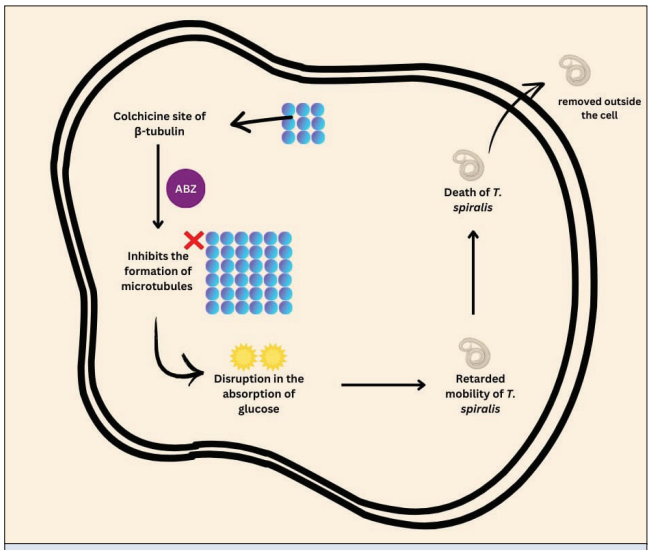

Fig 1. Basic mechanism of action of Albendazole against *T. spiralis*.ABZ: Albendazole

Multiple reports have been seen regarding the drug resistance and chemical drug residues of anthelmintics [31-33]. Drug resistance is the major emerging threat to the lives of humans as well as animals [34]. However, researchers are struggling hard to combat the resistance issue [35]. Because of the rising issue of drug resistance, scientists have focused on the development of alternative medicine therapy to cure the disease [36]. Alternative medicine strategies for the treatment of various diseases and infections include probiotics, prebiotics, herbal medicine, vaccines, immunogens, vitamins, peptides, etc. [37-41]. Among all the alternative medicine therapies, plant-based products are the best option because of their wide range of therapeutic effects [42-45]. Botanical compounds are safer and have more potent results against multiple parasitic diseases [46]. Plant-based compounds are well known for their various therapeutic and medicinal properties including antioxidative, anti-inflammatory, anti-infectious, immunomodulatory, and antimicrobial properties [47-50]. Some botanical compounds can be used directly as antimicrobial agents as they have a higher safety index and low side effects [51]. However, some compounds of plants are toxic to the vertebrates as well [52].

In this review, we will briefly discuss the control strategies for *T. spiralis* with the help of plant-based compounds. This review covers different botanical compounds that are derived from multiple plants including phenolics, tannins, and saponins. Detailed mechanisms of action of different botanical compounds will also be discussed. For a proper understanding of the control strategies and mechanism of action of botanical compounds, we must know the normal life cycle of *T. spiralis* and its pathogenesis.

Methodology

This review used Google Scholar *(www.scolar.google.com)* as the primary source of information. Furthermore, ResearchGate *(www.researchgate.com),* PubMed *(https://pubmed.ncbi.nlm.nih.gov/),* and ScienceDirect *(http://www.sciencedirect.com/)* were used as secondary search engines. Keywords used are "Botanicals", "*Trichinella spiralis*", "Food-borne zoonotic diseases", "Trichinosis", "*T. spiralis*", "Use of Botanical compounds for the control of *Trichinella spiralis*", and "Plants used for the control of *T. spiralis*". This is a qualitative review, so no statistical comparison was made, and the results are not quantified.

Life Cycle and Pathogenesis

The life cycle of *T. spiralis* contains 3 life stages which include newborn larvae, adult, and infective muscle larvae [53]. The primary hosts of *T. spiralis* are pigs and wild boars while the intermediate hosts include humans and other mammals [54,55]. The primary route of the transmission of the disease is through the consumption of contaminated meat [56,57]. However, vertical transmission of the disease is also reported in some cases [58]. After the ingestion of the meat contaminated with *T. spiralis,* the encysted larvae of the pathogen are released into the stomach and small intestine [57,59]. The larvae are released from their cysts after exposure to digestive enzymes (pepsin and gastric acid) [60]. The released larvae then invade into the small bowl mucosa. They take nutrients from the small intestine and become adults (male = 1.4-1.6 mm; female = 1.4-4 mm) [61,62]. The adult larvae in the small intestine reside there for about 4 weeks for mating and laying eggs [63]. Female nematode lays eggs after 1 week in the mucosal layer of the small intestine which then hatch into the larvae [60]. The hatched larvae enter the bloodstream and lymphatic system by penetrating the walls of the small intestine [64]. The newborn larvae enter the skeletal muscle cells from the bloodstream where they form nurse cell-

larvae complex [65]. Nurse cells protect the larvae from the host immune system and nourish them [66-68]. The larvae migrate to the striated muscles where they encyst *(Fig. 2)*. The encysted larvae remain dormant and may remain infectious for years [69].

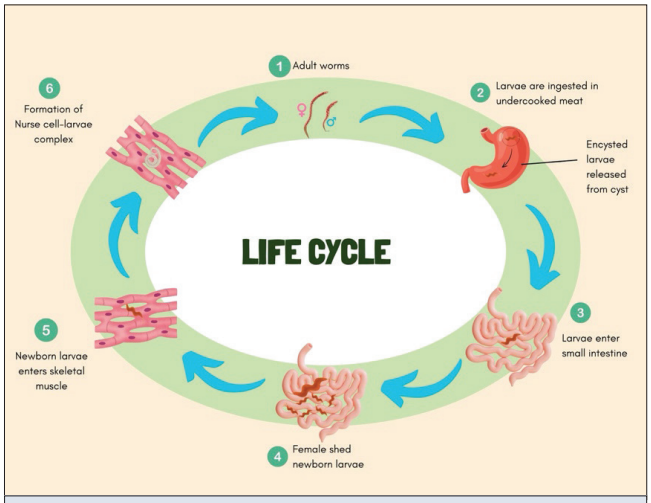

Fig 2. Life cycle of *T. spiralis*

Botanical Control

Naturally occurring plant-based compounds have been tested and proven effective for the treatment and control of multiple parasitic diseases [46,70-75]. Scientists are now focusing on the specific compounds of the plants instead of using whole parts (leaves, roots, bark, stem, and flowers) [76,77]. Botanical compounds have diverse medicinal and therapeutic properties including anti-inflammatory, antioxidant, anticancer, antimicrobial, immunomodulatory, antimutagenic, cardioprotective, neuroprotective, and antidiabetic activities [78-83]. This wide range of biological properties enables them to be used for the effective treatment and control of multiple diseases [84]. Botanical compounds are of very great concern to researchers because of the emerging threat of antimicrobial resistance [85]. Scientists are focused on the development of new drugs that have potent activity as an alternative to the previously existing antimicrobial drugs [86]. In this review, we will further discuss the activity of naturally occurring botanical compounds for the control of *T. spiralis*. For the development of new potent drugs from the botanical compounds, we are required to understand the mechanism of action of the botanical compounds. Details of multiple plant-based botanical compounds are given below:

Saponins

Saponin is a Latin word which is named because of the foamy/soapy quality when they are agitated with water [87]. Saponins are glycosides that have at least one glycosidic linkage between a glycone (sugar chain) and aglycone (non-sugar organic molecule) [88,89]. Saponins are most commonly used for the formation of soap, drug adjuvants, and for the synthesis of steroids [90]. Research has been conducted by multiple researchers to check the activity of saponins against *T. spiralis* [91]. Scientists have found potent results in the inhibition of *T. spiralis* by using saponin compounds [92-100].

Saponins have great potential to boost the immune response by stimulating chemokines and cytokines [101]. Saponins are responsible for regulating the recruitment of immune cells and intracellular signaling mechanisms [102]. They also aid in the proliferation and differentiation of T-cells into CD4+ T-helper cells [103]. Saponins have the ability to destroy *T. spiralis* due to their anti-inflammatory potential *(Fig. 3)*. TNF-α is a cytokine that is responsible for the regulation of other inflammatory cytokines [104]. Saponins depress the activity of TNF-α expression which will destroy *T. spiralis* [105]. However, severe destruction of newborns and adults of *T. spiralis* has been seen along with vesicular areas, loss of annulations, blebs, and marked swelling of the cuticle [91].

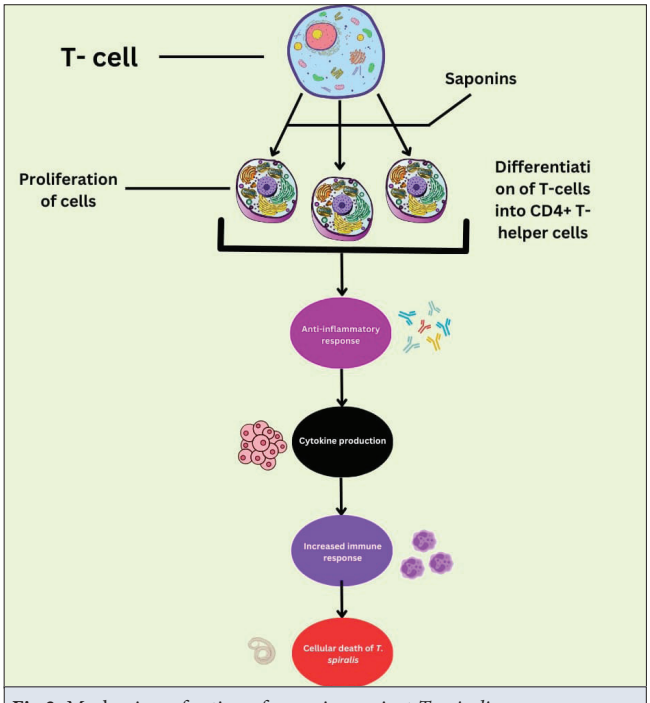

Fig 3. Mechanism of action of saponins against *T. spiralis*

Another mechanism of saponin has also been reported that saponins have the ability to alter the membrane permeability which will result in their cytostatic and cytotoxic activities [106-109]. This specific property of the saponins makes them able to destroy the pathogenic

Table 1. *Botanical Compounds used against T. spiralis and their mechanism of actions*

Sr. no.	Class of Compound	Compound Used	Plant Source	Investigation Medium	Organism Used	Mechanism of Action	Results	References
1	Saponins	Oleanolic-type triterpenoidal saponins	*Bassia indica*	*In vivo* & *in vitro*	Mice	Saponins act as an anti-inflammatory agent by depressing the TNF-α expression in the tissues of muscle	Severe destruction of *T. spiralis* newborn larvae and adult worms	[92]
		Triterpenoidal saponins	*Luffa aegyptiaca*	-do-	-do-	Increase the permeability of the cell membrane causing cytostatic and cytotoxic effects	Death of *T. spiralis* has been reported due to the altered membrane permeability and cytotoxic activity of the saponins	[91]
		Extract of *Holothuria polii* containing various saponin compounds	*Holothuria polii*	*In vivo*	-do-	-	The warm load has been decreased by 96.76% when *H. polii* extract was treated with albendazole	[93]
		Aqueous and alcoholic leaf extracts of *Tetradenia riparia* containing compounds of saponins	*Tetradenia riparia*	*In vitro*		-	The anthelminthic effect of saponins has been seen *in vitro* testing	[157]
2	Phenolics	Multiple phenolic compounds	*Bassia indica*	*In vitro* & *in vivo*	Mice	Anti-inflammatory response has been seen with the depression of TNF-α expression, resulting in the death of the parasite	Severe destruction of *T. spiralis* newborn larvae and adult worms	[92]
		Resveratrol	-	*In vitro*		-	Significant activity against newborn and adult *T. spiralis* has been seen. However, there is no activity seen against the muscle stage of the *T. spiralis*	[116]
		Ellagic acid (EA)	-	*In vivo*	Mice	EA increases catalase activities and decreases the nitric oxide in the muscular and intestinal tissues which will result in improving oxidative stress	EA has more potent results against the intestinal phase of *T. spiralis* as compared to the muscle phase	[117]
		Gallic acid	-	*In vivo*	Male mice	Gallic acid is a vigorous antioxidant, and it produces large amounts of free radicals which results in the lipid peroxidation process. Lipid peroxidation favors the condition to damage the cellular membranes of the parasite	When gallic acid is administered orally at the dose rate of 30 mg kg^{1}, the infection rate of *T. spiralis* is reduced at a noticeable amount as compared to the results of groups of mice treated with Albendazole	[118]

Table 1. *Botanical Compounds used against T. spiralis and their mechanism of actions (continued)*

Sr. no.	Class of Compound	Compound Used	Plant Source	Investigation Medium	Organism Used	Mechanism of Action	Results	References
3	Tannins	Extract containing various tannin compounds	*Luffa aegyptiaca*	*In vitro* & *in vivo*	Mice	Tannins increase the cellular permeability and reduce the CD34 expression[1]	Worms load has been reduced due to the altered cell membrane and reduction in the CD34 expression	[91]
		Tannic acid	-	*In vivo*	Swiss albino mice	-	Synergistic effects of tannic acid with Albendazole exhibit maximum activity against *T. spiralis.* However, tannic acid with a dose rate of 2000µg/ml has the same antiparasitic effects as Albendazole	[158]
		Dietary tannin compounds	Quebracho	*In vivo* & *in vitro*	Rats	-	Dietary quebracho tannins exhibited potent activity *in vitro.* However, no significant effects were seen in the small intestines of the rats	[159]
		Clove oil enriched with tannin compounds	-	*In Vitro*		Clove oil disrupts the folic acid cycle[2] or DNA synthesis of the parasite. However, clove oil significantly disrupts the metabolism of the parasite which results in the death or morphological changes in the parasite that hinders parasitic growth or multiplication	100% death of the adult worms was reported at the concentration of 50 µg/mL of clove oil. However, a significant change in the morphology of *T. spiralis* was reported at the concentration of 50 µg/mL	[160]
4	Others	Methanolic extract of *R. chalepensis*	*R. chalepensis*	*In vitro*		-	The n-hexane partition of the methanolic extract showed potent activity against *T. spiralis* with anLC_{50} value of 147.6 µg/mL	[119]
		Artemisinin	*Artemisia annua*	-	-	When the infected mice are treated with *A. annua* extract, the normal flora of the intestine is restored and the TGF-β expression was reduced	Adult worm count has been reduced in the intestinal tract of the infected animal	[120]

[1]*CD34 have the ability to inhibit cellular differentiation.*
[2]*Folic acid cycle plays a key role in the DNA synthesis of parasites. The folic acid cycle refers to the conversion of folic acid into tetrahydrofolate and dihydrofolate*

organism, i.e., *T. spiralis,* and can be used as a therapeutic agent [110]. However, to make new potent and safer drugs, more research must be conducted on the safety index of saponins.

Phenolics

Phenolics are the class of the compounds which have at least one hydroxyl group attached to the aromatic group of the hydrocarbons [111]. Phenolic compounds are classified on the basis of phenol units attached to the molecule [112, 113]. Phenolic compounds have multiple biological activities including enzyme inhibition, antioxidant, anti-cancer, and anti-inflammatory properties [114]. These properties make them able to be used as the cure for multiple diseases and conditions [115].

Phenolics have been reported effective in the control of *T. spiralis* by alleviating the inflammatory response [92,116-120].

The inflammatory response was increased because of the downregulation of IL-6 and increased expression of IL-10 in the tissues [121]. Phenolics can increase catalase activities and decrease the nitric oxide in the muscular and intestinal tissues which will result in improved oxidative stress [122,123]. Oxidative stress refers to an imbalance in the antioxidants and the free radicals which cause cellular death [124]. When the number of free radicals increases, it causes lipid peroxidation in the cell [125]. Lipid peroxidation provides a favorable environment to destroy the cellular membrane [126]. Oxidative stress plays a significant role in combating parasitic diseases by damaging the cells of the parasite [127]. In this condition, hosts use a large amount of reactive oxygen species, especially H_2O_2 to fight the developing parasitic disease [128]. However, some other mechanisms of action of phenolics are to disrupt the cell membrane and alter its permeability, denaturation of protein, and ion chelation (reaction between complexing agents which creates a ring structure and metal ions) [129-133].

Synthesis of novel drugs for the control and treatment of *T. spiralis* infection can be done with the help of understanding the mechanism of action of the commercial drugs and the comparative mechanism of the phenolic compounds [134]. However, there is still a need to do further research on the safety index of plant-based phenolic compounds.

Tannins

The term tannin refers to the abundance of oak bark compounds that were used for tanning the hides of the animals [135]. Tannins are large polyphenolic compounds that contain hydroxyls, carboxyl, or other suitable groups and make strong complex compounds with other macromolecules [136,137]. Tannins have a wide range of biological activities including anticancer, antioxidant, and anti-inflammatory properties [138-141]. However, multiple research projects have been made to check the effectiveness of tannin compounds for the control or treatment of various parasitic diseases [46,142-144].

Multiple research projects claimed the potent activity of tannins against *T. spiralis* [110,117,119,145]. Tannins have the ability to bind with the free available protein causing nutritional deficiency for *T. spiralis* [146]. The nutritional deficiency reportedly kills the larvae and adults of *T. spiralis* [147,148]. The activity of tannins against the cuticle of *T. spiralis* has more potent results because the cuticular structures are vital for the defense and nutritional role of the parasite [98,148-151]. However, another mechanism of action of tannins is also reported that tannin compounds disrupt the cellular metabolism of the parasite [152,153]. Tannins can cause disruption in the synthesis of DNA or the folic acid cycle [154-156]. In order to make new potent drugs for the treatment and control of *T. spiralis,* we must do further research on the safe administration of these compounds.

Conclusion

Trichinosis is a highly zoonotic disease of humans caused by *T. spiralis*. The disease is majorly transmitted through the consumption of raw or undercooked meat. Albendazole and mebendazole are two main anthelmintics that have been in use to treat trichinosis for a long time. Albendazole is a very effective drug in the early stages of the *T. spiralis* infection, but resistance has been reported multiple times. Drug resistance is the most prevailing issue that needs to be addressed as early as possible. Scientists have focused on the development of novel drugs for the treatment of *T. spiralis* infection. Botanical compounds have multiple medicinal and therapeutic properties which make them able to treat multiple parasitic diseases. Botanical compounds are considered as the best alternatives for the development of new drugs for the treatment and control of trichinosis. Multiple compounds have been tested against the newborn, larvae, and muscle stage of *T. spiralis*. Saponins, tannins, and phenolic acids have potent anthelminthic activity against trichinosis. However, synergistic activities of these botanical compounds with Albendazole have the highest activity in the reduction of the worm load. This review suggests further research on the safety index of effective botanical compounds to formulate novel drugs for the treatment and control of highly zoonotic trichinosis.

Declarations

Availability of Data and Materials: Data and materials for this research are available upon request.

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Competing Interests: The author declares that there is no conflict of interest.

Generative Artificial Intelligence: No Generative Artificial Intelligence was used in this reperch.

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