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Current Aspects in Trichinellosis

José Luis Muñoz-Carrillo, Claudia Maldonado-Tapia, Argelia López-Luna, José Jesús Muñoz-Escobedo, Juan Armando Flores-De La Torre and Alejandra Moreno-García

Abstract

Currently, it is estimated that more than 11 million humans in the world are infected by helminth parasites of Trichinella species, mainly by Trichinella spiralis (T. spiralis), responsible for causing Trichinellosis disease in both animals and humans. Trichinellosis is a cosmopolitan parasitic zoonotic disease, which has direct relevance to human and animal health, because it presents a constant and important challenge to the host’s immune system, especially through the intestinal tract. Currently, there is an intense investigation of new strategies in pharmacotherapy and immunotherapy against infection by *Trichinella spiralis*. In this chapter, we will present the most current aspects of biology, epidemiology, immunology, clinicopathology, pharmacotherapy and immunotherapy in Trichinellosis.

**Keywords:** Trichinellosis, immune response, pharmacotherapy, resiniferatoxin, immunotherapy

1. Introduction

Over 2 billion people are infected with helminth parasites worldwide [1, 2], making them one of the most prevalent infectious agents, responsible for many diseases in both animals and humans [3], thus being a public health problem throughout the world [4]. Research in these parasitic infections is of direct relevance to human and animal health [5], due to its capacity to cause great morbidity and socioeconomic loss [1]. In both humans and animals, helminth parasites establish chronic infections associated with significant downregulation of the immune response [6, 7], inducing a broad spectrum of pathological responses and clinical manifestations, which result in increased morbidity in affected individuals [1].
Trichinellosis is the parasitic disease caused by the parasitic helminth species of the genus *Trichinella* [8], which is a zoonotic parasitic disease, resulting from the consumption of meat from infected animals [9]. Currently, 12 species have been identified, which are classified into two clades: (1) the clade of the encapsulated species: *T. spiralis* (Figure 1), *T. native*, *T. britovi*, *T. nelsoni*, *T. murrelli* and *T. patagoniensis*, T6, T8 and T9 and (2) the clade of non-encapsulated species *T. pseudospiralis*, *T. papuae* and *T. zimbawensis* [11–13].

2. Epidemiological aspects of Trichinellosis

Trichinellosis is a parasitic disease, which is characterized by a wide range of hosts, including humans, mammals and birds, as well as a cosmopolitan disease because it has a wide geographical distribution [14–16]. Trichinellosis probably originated in wild animal populations of the Arctic and subarctic regions; later, it was extended to the animal populations of the temperate and tropical zones [17].

According to the World Health Organization (WHO) until the year 2009, there were more than 65,000 cases of Trichinellosis in the world, with more than 42 fatal cases [18] in the regions of Africa, South Asia, Europe [12, 19] and America, mainly United States, Mexico, Chile and Argentina [20], because of its high infectivity. However, it is estimated that currently 11 million humans in the world are infected by the *Trichinella* species, mainly by *T. spiralis* [18]. In 2014, Food and Agriculture Organization of the United Nations (FAO), together with the WHO, published a list of the top 10 food-borne parasites that affect the health of millions of people

![Figure 1](image-url)  
Figure 1. Infective larvae of *T. spiralis*. Photomicrograph of infective larvae of *T. spiralis*, from artificial digestion, observed at a 10× objective under the light optical microscope [10].
every year worldwide, infecting muscle tissues and organs and causing serious health problems. *T. spiralis* occupied the seventh place, below parasites of medical importance such as *Taenia solium* (*T. solium*), *Toxoplasma gondii* (*T. gondii*) and *Entamoeba histolytica* (*E. histolytica*); therefore, currently Trichinellosis remains a food-borne parasitic disease of great medical importance worldwide [21], and its impact and magnitude of the problem that this parasitic disease represents become evident only in the appearance of epidemic outbreaks [22].

In recent years, the reported rates of Trichinellosis in Mexico have been reduced to levels that are comparable to those of the United States. In fact, Canada now reports one of the highest rates in North America [23]. In Mexico, human Trichinellosis frequently occurs from the ingestion of raw or undercooked pork [9, 24]. In general, in Mexico, there is little knowledge of the disease, and in existing epidemiological studies by post-mortem histopathology of humans, prevalence of 50% has been observed, while in hospitals it is from 4 to 15% [25]. Since 1990 to date, more than 1122 cases of human Trichinellosis have been reported in at least 17 states of the country such as Aguascalientes, Chihuahua, Mexico City, Colima, Durango, State of Mexico, Guanajuato, Guerrero, Jalisco, Michoacán, Nuevo León, Oaxaca, Querétaro, San Luis Potosí, Veracruz and Zacatecas [25–27]. In Zacatecas, it has been considered as a zoonosis; since 1976, more than 100 cases have been reported in humans, pigs, dogs and domestic rats [28–30].

### 3. Biology of *Trichinella spiralis*

James Paget, a medical student at St. Bartholomew’s Hospital in London, England, observed a parasite in the diaphragm muscle of a 51-year-old Italian patient who had died from tuberculosis. Subsequently, the British zoologist Richard Owen in 1835 studied portions of muscle tissue of the Paget case and gave it the name of *T. spiralis* [31]. The adult parasites of *T. spiralis* were discovered by Rudolf Virchow in 1859 and Friedrich Zenker in 1860, who finally recognized the clinical importance of the infection and concluded that humans become infected by eating raw meat infected with the parasite [32].

The epidemic of this zoonosis is very particular, since the “domestic” and “wild” cycles of the *T. spiralis* have been clearly studied. But between them is the synanthropic cycle. In the domestic cycle (Figure 2), the main transmission vector to humans is the pig, through the ingestion of meat infected with *T. spiralis*. In the wild cycle, *T. spiralis* is kept in the environment by predatory and scavenger animals and can enter the domestic cycle accidentally. While in the synanthropic cycle, animals such as rats, cats, dogs, foxes, mustelids, among others, act as transmission vectors for the different *Trichinella* genotypes involved in any of the two mentioned cycles [33].

The main characteristic of the epidemiology of *T. spiralis* is its obligatory transmission by ingestion of infected meat [34, 35]. When a host ingests meat infected with L1 of *T. spiralis* (*T. spiralis*-L1), the digestive juices of the stomach dissolve the collagen capsule [36], also called nurse cell (NC), releasing the *T. spiralis*-L1, which travel to the small intestine, where they invade the columnar epithelium [37], giving rise to the intestinal phase of the infection (Figure 2).
After 10–30 hours post-infection (pi), *T. spiralis*-L1 mature to female and male adult worms (AD). Approximately 7 days pi, copulation occurs between female and male AD. Embryogenesis lasts about 90 hours, since the newborn larvae (NBL) of *T. spiralis* are released [38, 39]. These NBL of *T. spiralis* possess a stylet in their oral cavity, which they use to internalize within the epithelial cells of the host [36], penetrating the submucosa of the small intestine, migrating mainly through the circulatory system to various organs and subsequently invading the musculoskeletal cells, causing tissue damage (Figure 2). Only the NBL of *T. spiralis* that invade the musculoskeletal cells can survive and grow [15], giving rise to the muscle phase of the infection. During the muscular phase (Figure 2), the NBL of *T. spiralis* are in the muscle fibers, destroying them partially, and begin a period of post-embryonic development, growing and developing exponentially [36, 38, 39]. Approximately at 15 days pi, the formation of NC is induced with a fusiform or elongated aspect, containing in its interior one or several L1-*T. spiralis*, forming the NC-L1 complex [40]. The NC formation process is a complex process and includes the cellular response of the infected muscle (from differentiation with a complete loss of the myofibrillar organization, re-entry and arrest of the cell cycle in G2/M) and the responses of the NC (cells undergo activation, proliferation, redifferentiation and fusion processes with each other or with the infected muscle cell). Since the satellite cell is a progenitor cell located within the capsule wall, a new cell can be continuously delivered from the myoblast, even if the present NC dies. This explains why CN seems intact and active for years despite intracellular parasitism. In this way, the parasites use the muscular mechanisms of cellular repair of the host to establish parasitism [41]. *T. spiralis* develops its infectious stage approximately between days 21 and 30 pi, and six months after infection, the deposit of calcium begins in
the NC walls, calcifying in 1 year. L1-\textit{T. spiralis} can be retained for several years, depending on the host species. L1-\textit{T. spiralis} appears to be non-pathogenic for natural hosts except for humans [15, 42]. The main striated muscles where the L1-\textit{T. spiralis} is implanted are the most active such as the diaphragm, masseters, intercostals, eye muscles, muscles of the tongue, and anterior and posterior extremities (Figure 2) [43, 44].

4. Clinical pathology of Trichinellosis

The severity of the clinical disease is strongly dependent and directly correlated with the number of L1-\textit{T. spiralis} ingested, age, sex, invaded tissue, nutritional, hormonal and immune status. Likewise, the infection can give rise to a wide spectrum of clinical forms, from asymptomatic to mortality [14, 17, 45].

The clinical pathology of Trichinellosis can be divided based on the phases of the \textit{T. spiralis} life cycle (Figure 3). Infections with low parasite burden can remain asymptomatic, while high parasite burden can cause gastroenteritis associated with diarrhea and abdominal pain, approximately 24–48 hours pi (acute phase of infection) [46]. The intestinal phase of Trichinellosis is clinically manifested by the presence of signs, symptoms and gastrointestinal disorders, such as malaise, mild transient diarrhea, nausea, vomiting, abdominal pain, chills and fever, due to the invasion of L1-\textit{T. spiralis} and AD worms in the intestinal mucosa (Figure 3). These signs and symptoms usually persist from the first to the third week pi, depending on the dose of L1-\textit{T. spiralis} and the severity of the disease. From 2 to 6 weeks pi, the intestinal phase is still present, but the signs and symptoms that correlate with the intestinal disease decrease and the signs and symptoms of the migration phase appear [14, 38, 42, 47].

During the migration of NBL of \textit{T. spiralis}, which starts approximately 1 week pi and may last for several weeks [36], the first signs and symptoms to be clinically detected usually include myalgia, high fever, chills, a state like paralysis, periorbital and/or facial edema, conjunctivitis, pain, skin rashes, etc. (Figure 3) [14, 38, 42]. Other signs and symptoms are conjunctivitis including subconjunctival hemorrhages, headache, dry cough, petechial hemorrhages and painful movement disorder of the eye muscles. Some patients present urticaria, maculopapular rash and subungual hemorrhages, caused by vasculitis, the main pathological process of Trichinellosis [14]. Laboratory studies reveal a moderate increase in white blood cells (12,000–15,000 cells/mm$^3$), and circulating eosinophilia ranging from 5 to 50% [35, 45].

During the muscular phase of Trichinellosis, signs and symptoms such as myalgias, arthralgia, headache, periorbital and facial edema appear (Figure 3) [42]. The damage of the muscular cell stimulates the infiltration of inflammatory cells, mainly eosinophils. A correlation between levels of eosinophils and serum muscle enzymes, such as lactate dehydrogenase (LDH) and creatine phosphokinase (CPK), has been observed in patients with Trichinellosis, suggesting that muscle damage may be mediated indirectly by these activated granulocytes [14]. Thus, progressive eosinophilia is the most relevant clinical finding of the muscular phase of Trichinellosis [42]. The invasion of the diaphragm and accessory muscles of respiration by the parasite results in dyspnea [36]. In the chronic phase of the Trichinellosis after 4 weeks pi, a series of complications such as encephalitis, bronchopneumonia and sepsis arise. Chronic
Figure 3. Clinical pathology of Trichinellosis. Main clinical signs and symptoms of Trichinellosis. Intestinal phase (green), migration phase (blue) and muscular phase (red). This figure was made by the authors based on the references cited in the text.
Trichinellosis can cause persistent tingling, numbness and excessive sweating, as well as deterioration of muscle strength and conjunctivitis, which can persist up to 10 years in people who had not been treated early in the acute phase of the infection [14].

5. Immune response against *Trichinella spiralis*

In each phase of the life cycle of *T. spiralis*, different antigenic components are produced, which directly influence the host’s immune response [48] and are very useful in the diagnosis of Trichinellosis in both humans and animals. These antigens, *T. spiralis* larvae group (TSL)-1, are secreted and/or excreted by the L1-*T. spiralis* at the beginning of the intestinal phase and again in the muscular phase of the infection when the NC is formed [49–51]. The antigens TSL-1 are glycoproteins 43 [52–55], 53 [56–59] and 45 [60, 61] kDa, which are targets of antibodies that mediate humoral immunity against *T. spiralis*, which recognize their residues of tivelosa [51, 59, 62]. These TSL-1 antigens induce the maturation and activation of dendritic cells, which leads to the presentation of antigen, through the expression of the major histocompatibility complex (MHC) class II [63, 64], promoting the development of the Th1 type immune response [48], with the subsequent predominance of a Th2 type immune response, resulting in a mixture of both Th1/Th2 immune responses, dependent on the CD4⁺ T cells (Figure 4) [65, 66].

The Th1 type immune response against *T. spiralis* is characterized by a significant increase in Th1 cytokines such as IL-12 [67–69], INF-γ [48, 67–70], IL-1β [69, 71] and TNF-α (Figure 4) [67–69, 72]. In recent years, studies have shown that the production of Th1 cytokines is directly associated with the development of the inflammatory response and intestinal pathology, which favors the infection by *T. spiralis*. IL-12 and INF-γ participate in the polarization of the Th1 immune response [48, 67, 68]. IL-12 promotes the differentiation of naïve T cells to a Th1 phenotype that produces INF-γ [73], which induces the expression of MHC II molecules in dendritic cells [74], increases the development and differentiation of Th1 cells, induces the expression of transcription factors such as nuclear factor (NF)-κB [75] and regulates the production of proinflammatory cytokines [76, 77]. However, exogenous administration of IL-12 in *T. spiralis* infection suppresses intestinal mastocytosis, delaying the expulsion of the parasite and increasing the parasitic muscle burden [78]. TNF-α is a potent proinflammatory cytokine [79], which plays a key role in the pathogenesis of inflammatory diseases, since it participates in the activation of a cascade of proinflammatory cytokines, such as IL-1β [79–81]. Studies have shown that the production of TNF-α during infection by *T. spiralis* is associated with the development of intestinal pathology [72, 82–84]. TNF-α also induces the expression of iNOS and consequently NO production [85–88], which acts mainly as an effector molecule in against both extracellular and intracellular parasites [89]. Studies have shown that TSL-1 antigens are capable to induce the expression of iNOS with the consequent production of NO [90]. However, NO production is also associated with the development of intestinal pathology in *T. spiralis* infection [72, 91]. Finally, IL-1β is a proinflammatory cytokine [92, 93], which is produced during infection by *T. spiralis*, participating in the inflammatory bowel response. However, until now, its function is not well known [69, 71].
On the other hand, TSL-1 antigens are capable of activating dendritic cells and CD4+ T cells [63, 94], inducing the synthesis of Th2 cytokines such as IL-4, IL-5, IL-10 and IL-13 (Figure 4) [48, 67, 68, 70, 95–97]. IL-4 and IL-5 [98] are a critical factor in the terminal differentiation and proliferation of eosinophils, which are involved in the development of intestinal pathology, thus promoting the inflammatory response during infection by *T. spiralis* [14, 99]. IL-4 plays a central role in regulating the differentiation of antigen-stimulated naïve T cells, causing such cells to develop into Th2 cells capable of producing IL-4 and several other Th2 cytokines including IL-5, IL-10 and IL-13. In addition, it suppresses potently the production of INF-γ [100, 101]. IL-10 is a cytokine of great importance during infection by *T. spiralis*, which decreases the production of IL-12, IFN-γ and the proliferation and presentation of antigens of dendritic cells, polarizing the immune response to Th2 type [65, 102]. Since the absence or decrease of IL-10 significantly delays the intestinal expulsion of *T. spiralis*, increasing the muscular parasite burden [78]. IL-13 is also a cytokine produced by Th2 cells, which has direct effects on eosinophils, including the promotion of their survival, activation and recruitment [103–105]. The synthesis and release of IL-4 and IL-13 induce B cell proliferation and the expression of surface antigens, including the CD23 receptor (FcεRII) of low affinity to IgE and MHC class II molecules, stimulating the production of IgE [106, 107]; inducing hyperplasia of mast cells and eosinophils, which triggers immediate hypersensitivity reactions [108–110]; rapidly expanding in the mucosa, predominantly within the epithelium [63], where the TSL-1 antigens can directly induce their degranulation; and promoting the expulsion of *T. spiralis* from the intestine [51]. Studies in mice deficient in IL-4/IL-13 showed a reduction in the expulsion of *T. spiralis* and mastocytosis, showing development of intestinal pathology [82, 83, 111].
6. Diagnosis of Trichinellosis

The early clinical diagnosis of Trichinellosis is quite difficult due to the lack of symptoms and pathognomonic signs. In addition, chronic forms of the disease are not easy to diagnose [14]. When the infection occurs in epizootic or outbreak form, its diagnosis is easier. However, it is difficult in low-level or sporadic infections, since the clinical picture is usually common to many other enteric diseases. This makes it necessary to carry out a differential diagnosis [34]. The diagnosis of Trichinellosis must be based on three main criteria: (1) clinical findings—recognition of signs and symptoms; (2) laboratory parameters, such as eosinophilia and muscle enzymes, detection of antibodies and/or detection of L1- *T. spiralis* in muscle biopsy and (3) epidemiological research—identification of the source and origin of the infection and outbreak studies [14].

Identification of L1- *T. spiralis* in muscle tissue is the positive diagnosis of the disease; any technique used for this purpose is included within the so-called Direct Diagnostic Methods [42], which performed post-mortem and includes four main techniques: (1) plate compression [72], (2) polymerase chain reaction (PCR) [14, 36], (3) artificial or enzymatic digestion [72] and (4) histology [24]. The detection of antibodies against *T. spiralis* in the host represents a solid evidence of contact with the parasite, and the techniques developed for that purpose are included among the Indirect Diagnostic Methods [42], through which they are detected antibodies against *T. spiralis* antigens. Among which we find (1) indirect immunofluorescence [112], (2) enzyme-linked immunosorbent assay (ELISA), (3) Western blot [113] and 4) micro-immunodiffusion double [40].

7. Treatment of Trichinellosis

7.1. Pharmacotherapy

Pharmacotherapy used in Trichinellosis includes the use of antiparasitic and steroidal anti-inflammatory drugs [114]. Currently, the antiparasitic treatment used for Trichinellosis is the administration of benzimidazoles, mainly albendazole and mebendazole, which are effective against the parasite [40, 115]. In addition, different antiparasitic drugs such as ivermectin, nitazoxanide, quinfaamide and flubendazole have been evaluated, and favorable results have been observed [40, 116]. These drugs are the most effective therapies at the beginning of the disease, since they kill the adult parasites. Although albendazole is better tolerated, a recent research showed that thiabendazole was a potent and curable drug because its efficacy was almost 100% to eliminate intestinal worms [117].

Respect to pharmacotherapy with steroidal anti-inflammatory drugs, glucocorticoids (GC) are the most used for the treatment of signs and symptoms of the inflammatory response produced by the *T. spiralis* infection [118, 119]. GC are potent anti-inflammatory drugs, which regulate transcriptional pathways in diverse cellular contexts such as development, homeostasis, metabolism and inflammation [120]. GC exert their anti-inflammatory activity primarily in two ways: (1) induce the expression of several genes that encode proteins that exert anti-
inflammatory effects such as the leukocyte-inhibitory secretory protein, the inhibitor of NF-κB (IκB-α), IL-10 and the IL-1 antagonist receptor [121, 122]; (2) inhibit the expression of proinflammatory genes by suppression of transcription factors, such as NF-κB [123] and activating protein (AP)-1 [120], through the protein-protein interaction [124], regulating the inflammatory cytokines expression, such as TNF-α, IL-1α, IL-1β, IL-8, IFN-α and IFN-β, and inflammatory enzymes such as iNOS, cyclooxygenase (COX)-2, inducible phospholipase A2 (cPLA2), adhesion molecules and inflammatory receptors [125, 126].

Although GCs are potent anti-inflammatory drugs, their therapeutic use in Trichinellosis is limited [127], since research in recent years has shown that treatment with betamethasone [128] and dexamethasone [129] increases the parasitic load at the muscular level. Recently, studies showed that treatment with dexamethasone in the intestinal phase of *T. spiralis* infection inhibited the production of inflammatory mediators, such as PGE₂, NO, TNF-α, IL-1β, IL-12 and INF-γ, decreasing the number of eosinophils in the blood and the development of intestinal pathology. However, in the muscular phase, the implantation and parasite burden of L1-*T. spiralis* increased significantly [69, 72].

Given this therapeutic problem, new pharmacological strategies have been developed in the use of new anti-inflammatory drugs, which help to inhibit the inflammatory response during Trichinellosis, without the GC side effects. Resiniferatoxin is a vanilloid derived from the cactus plant *Euphoria resinifera*, an agonist of the transient receptor potential vanilloid (TRPV)-1 [130], which activates and then desensitizes the TRPV1 receptor producing an analgesic effect [131, 132]. Studies in both models *in vitro* and *in vivo* have shown that resiniferatoxin has an important anti-inflammatory activity, inhibiting the expression of NF-κB [133], iNOS and COX-2 [134], and the synthesis of PGE₂, NO and TNF-α [135, 136]. Finally, recent studies showed that treatment with resiniferatoxin during the intestinal phase of infection by *T. spiralis* decreased the levels of PGE₂, NO, TNF-α, IL-1β, IL-12 and INF-γ, as well as the number of eosinophils in blood. While in the muscular phase of *T. spiralis* infection, treatment with resiniferatoxin significantly decreased implantation and parasite burden of L1-*T. spiralis* [69, 72]. These findings suggest that resiniferatoxin may be a potential drug in the treatment of inflammatory diseases.

### 7.2. Immunotherapy

In immunotherapy during Trichinellosis, total and immunodominant antigens have been used, which activate the immune system of the host, causing a decrease in parasite burden in the intestine, affecting the fecundity of adult female worms, thus impacting the parasite burden on muscle tissue [137, 138]. Studies have shown that immunotherapy with *T. spiralis* total soluble (TS) antigen in murine experimental models induces protection, since a decrease in muscle parasite burden was observed [139]. In a study based on pig model infected with *T. spiralis*, to which immunotherapy was applied with *T. spiralis* TS antigen, antigens were identified in a molecular weight range of 14–97 kDa. Immunotherapy with *T. spiralis* TS antigen provoked a primary immune response, with a reduction in parasite burden, as well as damage to CN in the muscular phase of the infection, compared with the control group (without immunotherapy) [140].

On the other hand, TS and 45 kDa antigens of *T. spiralis* have been used [141], obtaining a greater protective effect on the part of the 45 kDa antigen, since it was observed alteration of
the NC. Thus, 45-kDa immunodominant antigen has been shown to be the most effective antigen against *T. spiralis* infection [142]. However, research with this immunodominant antigen continues to be viable as a vaccine in the future.

Immunization with 45 kDa antigens of *T. spiralis* has produced important effects on the immune response in the murine model, such is the case of immunization applied in rats with different nutritional conditions, which showed decreased parasite burden compared to controls becoming null in the nourished rats. In this study, *T. spiralis* TS antigen was applied in nourished and malnourished rats, which decreased the parasite burden in comparison with controls without treatment, observing lower parasite burden in nourished rats. *T. spiralis* TS antigen provoked an immune response against the L1-*T. spiralis*, since not only decreases the parasite burden but also causes changes at the histological level of the NC and prevented the implant, as occurred in the immunization with the 45-kDa antigen in nourished rats, conferring a high level of protection [141]. Similarly, in another study applying immunotherapy with TS and 45 kDa antigens of *T. spiralis*, a reduction in parasite burden was observed [16, 112].

A study in a rat model, in which the sublingual immunization treatment was applied with *T. spiralis* TS antigen, vehicle for sublingual immunotherapy (VSIT) and polyvalent bacterial vaccine, a protection against the infection of *T. spiralis* was observed [143]. Currently, adjuvants are substances that stimulate or improve the immune response against an antigen, without having a specific antigenic effect by themselves. The function of the adjuvant is determinant to achieve an adequate immune response. Encouraging results have been obtained in immunotherapy with the 45 kDa antigen adding an adjuvant. For what is believed to be a good therapeutic alternative through the sublingual route for the treatment of Trichinellosis.

8. Conclusion

Currently, Trichinellosis is a reemerging zoonotic parasitic disease that continues to affect the health of both animals and humans worldwide. For this reason, it is important to know well the biology of its etiological agent *Trichinella*, as well as its mechanisms of evasion of the host’s immune system, with the purpose of making a timely and differential diagnosis, to achieve a good treatment. Simultaneously, it is necessary to continue investigating therapeutic strategies that, through pharmacotherapy and immunotherapy, develop specific treatments directed to the parasite, avoiding collateral effects to the host.

Acknowledgements

Thanks to the authors who collaborated in the writing of this chapter: Dr. José Luis Muñoz, Claudia Maldonado, Argelia López, José Jesús Muñoz, Juan Armando Flores and Alejandra Moreno, as well as the Universities involved: Cuauhtémoc University Aguascalientes and Autonomous University of Zacatecas. Thanks for the financial support for chapter publication.
**Conflict of interest**

We have no conflict of interest related to this work.

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