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Trichinella spiralis as a Potential Antitumor Agent: An Update

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ABSTRACT

Due to the limited success of therapeutic strategies in treating tumors, a new practical potent approach is needed. This review aimed to investigate previous literature related to tumors and *Trichinella spiralis (T. spiralis*). In recent years, there has been growing interest in utilizing biological, viral, bacterial, yeast, and parasitic agents to cure cancers. According to several studies, some parasites could interferee with the tumors' growth. There has been much discussion about some parasites' applications to cure tumors in animals and humans. In studies, *T. spiralis* was found to have antitumor properties. The active proteins in *T. spiralis*, such as Caveolin-1, Heat shock proteins, and Ribosomal proteins, are thought to inhibit the growth of cancers, such as melanoma, myeloma, sarcoma, leukemia, stomach cancer, colon cancer, breast cancer, and lung cancer. In addition, these proteins are thought to induce apoptosis in specific neoplastic cells. Accordingly, antigens derived from parasites may be helpful in cancer immunotherapy. However, there are still many unanswered questions regarding *Trichinella spiralis'* potential use as a biotherapy agent against cancer. Future studies should focus on the purification of parasite antigens and their use for wider-scale trials in animal models.

Keywords: Antitumor, Apoptosis, Cancer, Immunotherapy, *Trichinella spiralis*

INTRODUCTION

Malignant tumors are one of the most threatening issues concerning people's well-being and are responsible for many human deaths (Carneiro and El-Deiry, 2020). Immunotherapy is a new approach in the field of oncology that confronts cancerous tumors by amplifying natural antitumor defenses (Schirrmacher, 2019; Wu et al., 2020). Detection of tumor antigens indicates that immunotherapy may be beneficial by stimulating the immune system's tumor suppressor mechanisms, and does not have side effects of chemotherapy or surgery (Harrington et al., 2019; O'Donnell et al., 2019). Cancer patients show early treatment improvement with autologous and allogeneic tumor cell vaccines (Pallerla et al., 2021). Many obstacles can hamper clinical success. These obstacles include inadequate antigenic natures, immune tolerance, and active immune evasion mechanisms used by progressing tumors to circumvent the immune system (Martin et al., 2020; Jhunjhunwala et al., 2021). The body's immune system must be stimulated to develop a new cancer treatment (Mulder et al., 2019). Furthermore, the immune system must be ready to attack cancer cells individually (Netea et al., 2020). This specificity will enable the immune system to overcome these obstacles (Bassiony et al., 2020).

The concept of tumor biotherapy has been developed as a clinical strategy for cancer treatment. It aims at suppressing or eradicating tumors using biological agents as therapeutic tools. Examples of these therapies include cytokines, monoclonal antibodies, growth factors, differentiation factors, cancer gene therapy, and antitumor bioactive materials (Kelley and Greten, 2021).

Several parasitic infections have been shown to induce antitumor activity in both laboratory animals and humans (Callejas et al., 2018; Daneshpour et al., 2019; Hu et al., 2019; Berriel et al., 2021). To justify this claim, a documented negative correlation has been established between the prevalence of some parasitic infections and cancer cases (Krementsov, 2009). Some cancer patients infested with certain parasites have reported a much longer lifespan than those who were not (Suresh et al., 2005). However, it is not feasible to activate the anticancer response through parasitic infections due to the morbidity and virulence of parasites. The administration of live vaccines containing non-pathogenic parasites could be an appropriate alternative (Kurup and Thomas, 2020). Acquired and innate immunity, anti-angiogenesis properties, increased cell apoptosis, and common antigen presentation may all contribute to tumor resistance induced by parasites (Albini et al., 2018). Mucins play a critical role in maintaining mucosal homeostasis and are responsible for the differential effector and regulatory responses against many microorganisms, including

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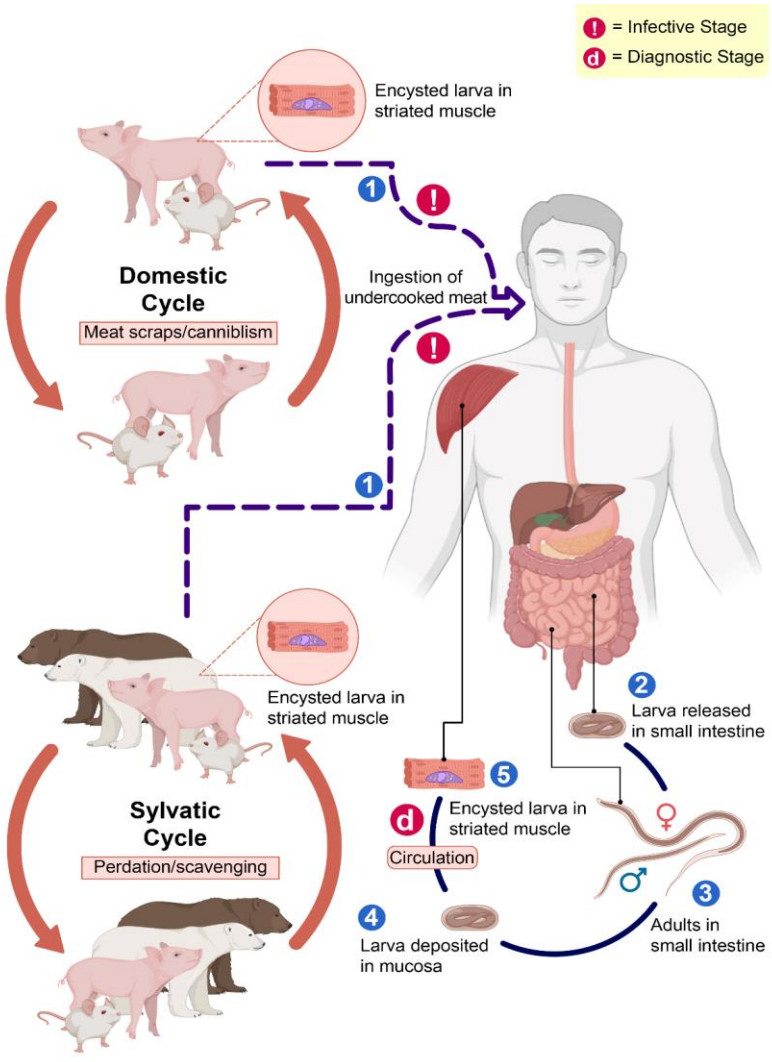
commensals and parasites (Dharmani et al., 2009). It has been found that several parasites share mucin-type O-glycan compounds, which are common antigens between cancer cells and parasites (Tarp and Clausen, 2008; Darani and Yousefi, 2012; Grondin et al., 2020).

In addition, parasites with high amounts of glycosylated antigens like *Echinococcus granulosus* may demonstrate superior anticancer effects against immune tolerance of cancer (Berois et al., 2022).

The active proteins in *T. spiralis*, such as Caveolin-1, Heat shock proteins, and Ribosomal proteins, inhibit cancers, such as melanoma, myeloma, sarcoma, leukemia, stomach cancer, colon cancer, breast cancer, and lung cancer (Kang et al., 2013; Liao et al., 2018). It is not yet known how *T. spiralis* inhibits tumor growth. The intestinal phase of *T. spiralis* is an example of a complex multicellular organism, and its potential to induce a T helper 2 (Th2) immune response is matchless (Ilic et al., 2012). It also secretes lipids, proteins, and metabolites that the immune system recognizes. So, the proliferation, differentiation, and activation of natural killer cells, cytotoxic T cells, and macrophages could be stimulated by *T. spiralis* infection (Zhang et al., 2018; Wang et al., 2020; Sun et al., 2022). Therefore, they would secrete elevated amounts of interleukins, interferons, transfer growth factor, tumor necrosis factor, and colony-stimulating factor (Fabre et al., 2009; Ilic et al., 2011). *In vivo* could activate macrophages to produce oncolytic molecules that kill tumor cells directly (Khan, 2008; Liu et al., 2015). Inhibiting the metastasis and proliferation of neoplastic tumors, Natural Killer (NK) cells serve as the primary defense against tumorigenesis (Pachynski et al., 2012; Smyth et al., 2002). When mice are infected with *T. spiralis* during the early muscle stage, NK cells trigger a cytotoxicity reaction *in vivo* (Patel et al., 2009). Interferon-Gamma (IFN-γ) and Tumour Necrosis Factor alpha (TNF-α) are two of the most potent pro-inflammatory cytokines with a wide range of biological activities (Boshtam et al., 2017; Shapouri-Moghaddam et al., 2018). The IFN-γ and TNF-α can cause tumor cells to necrosis and directly induce apoptosis within them in addition to vascular destruction around neoplasms (Chawla-Sarkar et al., 2003; Cruceriu et al., 2020; van Horssen et al., 2006). Cluster of Differentiation 8+ (CD8+) T cells can be cytotoxic when exposed to Interleukin 10 (IL-10), which has an antitumor function (Gu et al., 2017). Mouse models of tumors with CD8+T cells expressed with IL-10 have been shown to suppress tumor growth by producing higher amounts of IFN-γ (Jarnicki et al., 2006; Ruffell et al., 2014). IL-12 can also kill primary and metastatic tumors via the T helper 1 (T1) reaction and the promoted activation of CD8+T cells (Paijens et al., 2021). Consequently, cellular immune function, mediated by Th1 cells, suppresses malignant cell proliferation and angiogenesis. This review aimed to examine previous literature investigating the relations between *T. spiralis* and tumors.



General features of *Trichinella spiralis*

The *T. spiralis* is a widely distributed food-borne parasite that could trigger antitumor immunity by modulating immune system activity (Liao et al., 2018). *T. spiralis* is an obligate intracellular parasite that causes trichinosis in humans and many animals (Gottstein et al., 2009). Excretory-secretory proteins (ESPs) are complex proteins produced by *T. spiralis* during infestation (Babal et al., 2011). It is believed that polypeptide proteins, as well as ESPs, may inhibit tumor growth during the life cycle of *T. spiralis*, which includes the muscle larva (ML), the newborn larva (NBL), and the adult worm (AD, Romaris et al., 2002). The muscle larva has a more significant effect on enhancing host immunity because it lives longer, compared to the newborn and adult stages (Hewitson et al., 2009). Besides, ML is more accessible to collect than NBL or AD (Figure 1).

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***Trichinella spiralis* proteins**

Translationally controlled tumor protein

Recently some studies demonstrated that Translationally Controlled Tumor Protein (TCTP) has a high conservation level and is an abundant protein across various eukaryotic organisms (Bommer and Thiele, 2004). In tumor reversion, this protein is significantly downregulated (Bommer, 2017). It has been shown that factors, including cell cycle progression, histamine-releasing factors, malignant transformation, antiapoptotic, immunomodulatory functions, and calcium-binding proteins, play a crucial role in cell growth. Translationally controlled tumor protein has been found in *Plasmodium* subspecies and trematodes, and also some parasitic worm species, such as *Trichinella* (Mak et al., 2007; Nagano et al., 2009).

Caveolin-1

The caveolin-1 protein (*cav-1*) is part of the caveolae, which are introversions of the cells' plasma membrane in the form of flasks (Raja et al., 2019; Gokani and Bhatt, 2022). In some cancers, *Cav-1* causes apoptosis and cell cycle arrest at the first stages of tumorigenesis (Volonte and Galbiati, 2020; Arfin et al., 2021). Suppression Subtractive Hybridization (SSH) technique has been used to clone the *cav-1* gene from *T. spiralis* as an adult-specific antigen, which has been demonstrated to be extracted from maturing embryos and oocytes of this parasite (Wu et al., 2021).

Heat shock proteins

In addition to regulating cell growth, survival, and differentiation, heat shock proteins (HSPs) play an active role in the flexibility, intracellular arrangement, and proteolytic turnover of cells (Villesen et al., 2020; Karamanos et al., 2021; Lang et al., 2021). They are considered powerful immunoadjuvants that can lead to more substantial antitumor impacts (Banstola et al., 2020). Heat-inducible proteins, including sHSP, HSP60, HSP70, and histone H3, have been isolated from ES products and somatic extracts of *T. spiralis*, (Sun et al., 2018; Grzelak et al., 2020; Grzelak et al., 2022). Thw HSPs prevent cell death in *T. spiralis* and sustain homeostasis (Bolhassani and Agi, 2019).

Ribosomal proteins

Ribosomal proteins are essential for repairing DNA structure, cell differentiation, and development, generally overexpressed in cancers, such as esophageal, gastric, liver, and colorectal cancer (Mao-De and Jing, 2007; Abraham and Meltzer, 2017; Xie et al., 2018). The use of iRNA therapy within the past 30 years could help researchers treat many types of tumors and tumorigenic viruses with iRNA (Soudyab et al., 2016). There is still an underlying mystery regarding iRNA therapy since other novel cancer immunotherapies have emerged, and the fact that iRNA therapy has not been as practical and valuable as initially believed; therefore, it is unclear how it works (Taghikhani et al., 2020; Di Martino et al., 2021). A recent study of BALB/c mice showed that *Trichinella* iRNA significantly reduced the growth of mouse myeloma tumors (SP2/0). *Trichinella spiralis* also contains two ribosomal proteins, S24 and S24e, involved in DNA repair, cell growth regulation, and cell differentiation and are overexpressed in different types of cancer including gastric, colorectal, esophageal, and liver cancer (Duan et al., 2013).

Tropomyosins

Tropomyosins (Tms) are the core components of microfilaments (or actin filaments), which are the thinnest filaments of the cytoskeleton (Karabinos, 2019). Many eukaryotes contain Tms, which are acidic proteins found in yeasts, worms, flies, crustaceans, frogs, birds, and mammals (Gunning et al., 2008; Choi et al., 2012; Jeong and Park, 2020). A number of studies have demonstrated that Tms suppress both breast and bladder cancer as well as astrocytoma, central nervous system tumors, and colon cancers (Helfman et al., 2008; Humayun-Zakaria et al., 2019). An antitumor response was observed in SP2/0 myeloma cells with *T. spiralis* associated antigen, which could also stimulate cross-protective immunity against the tumor (Gong et al., 2011).

The prevention and treatment effects of *Trichinella spiralis* on cancers

Theantitumorr properties of *T. spiralis* have been demonstrated in numerous studies. It was first described in the 1970s that *T. spiralis* had an antitumor effect (Weatherly, 1970). Nevertheless, only limited progress has been made in this field due to inconsistent research. In this regard, it remains unclear how these inhibitory effects are acted. Furthermore, clinical trials have not provided compelling evidence linking *T. spiralis* to the prevention or treatment of tumors. There is also evidence that *T. spiralis* may trigger or contribute to tumor coinfections which mainly include viral, fungal, and bacterial infections (Hu et al., 2021). *Trichinella spiralis'* antitumor effect is not only attributed to increased innate immune function but may also be due to excretory-secretory (ES), which are complex proteins produced by *T. spiralis* during the infestation may have some antitumor effects indirectly by changing the expression of a tumor gene or directly by affecting antitumor activity including the apoptosis, immunomodulatory and anti-inflammatory effects which suppress the tumor growth (Sofronic-Milosavljevic et al., 2015; Vasilev et al., 2015; Ding et al., 2020b, Figure 2).

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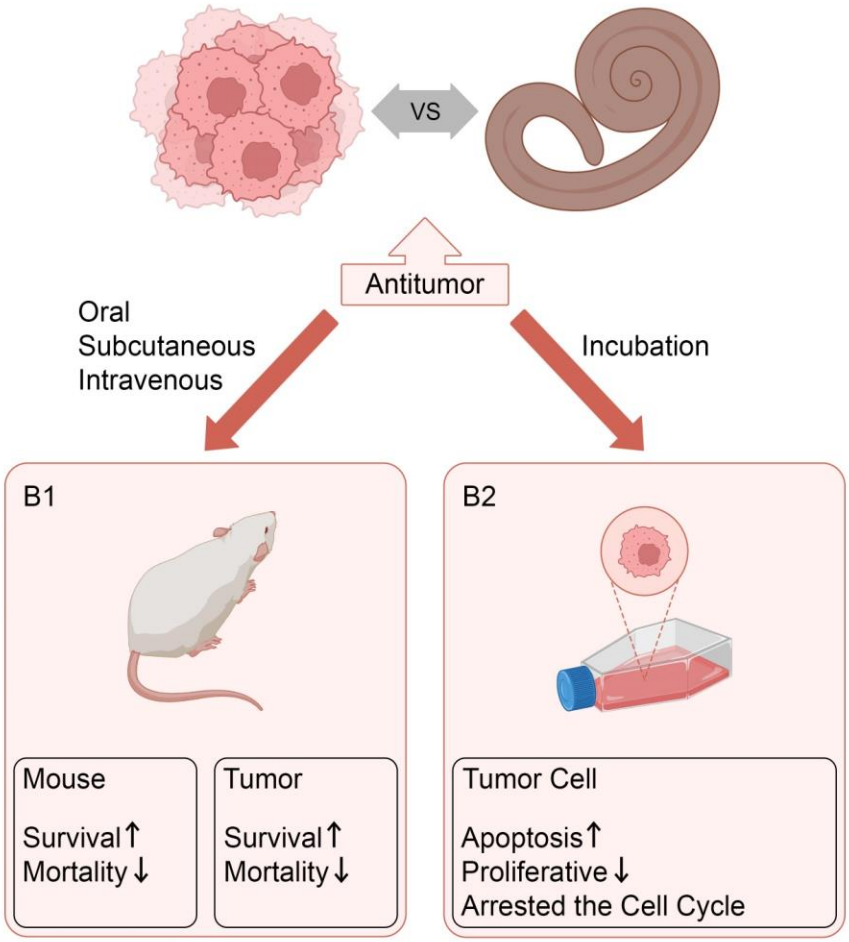

Figure 2. Relations between *T. spiralis* and tumors

Hepatocellular carcinoma

The sixth most prevalent type of cancer is hepatocellular carcinoma (HCC) in humans and animals (Balogh et al., 2016; Heimbach et al., 2018). The prognosis for HCC is driven by the tumor stage, with curative options providing a 5-year survival exceeding 70% for early-stage HCC compared with a median survival of ~1–1.5 years for symptomatic advanced-stage cases treated with systemic therapies (Villanueva, 2019). HCC is an aggressive and highly malignant tumor with a survival rate of less than 5% in 5 years (Grandhi et al., 2016). Available treatment methods have only been effective in some patients. Due to the high mortality rate and high risk of recurrence after treatment, new treatment methods are mandatory (Ringelhan et al., 2018; McGlynn et al., 2021). The regulatory mechanism of *T. spiralis* nurse cell formation is similar to tumor cell apoptosis signal regulation (Elhasawy et al., 2021). *Trichinella spiralis* nurse cell formation is a complex process and involves differentiation and cell cycle arrest of infected muscle cells. In other words, the nurse cell formation apoptotic pathways may be activated by antitumor genes that can suppress cell proliferation or induce apoptosis of the tumor cells (Wang et al., 2009). Although several parasites have been described for their ability to fight tumors, *T. spiralis* has proven particularly effective in cancer immunotherapy (Dabrowska et al., 2008). Many cytokines produced by T. spiralis are capable of inhibiting tumor growth. In addition, skeletal muscle cells are affected by *T. spiralis* infection during nurse cell formation, causing various changes (Dabrowska et al., 2016). As a result of these changes, muscle cells begin to differentiate, and apoptosis occurs, then the infected cells are stopped in the G2/M phase of the cell cycle (Wang et al., 2013). Additionally, *T. spiralis* and its extract inhibit tumor growth and induce apoptosis in tumor cells by stimulating mitochondrial pathways and death receptor pathways and apoptosis-related genes (Ding et al., 2020a; Ding et al., 2021). As part of the immune response to *T. spiralis* infection, the expression of c-Ski protein (a tumor suppressor protein) and genes associated with signaling pathways such as *p53* (apoptosis genes are expressed), *SMAD2*, and *SMAD4* are activated (Zakeri, 2017; Boros et al., 2019). These changes occur simultaneously with the increased activity of apoptosis factors involved in a mitochondrial pathway, such as caspase 9 and Bcl-2 associated protein X (BAX), as well as a death receptors pathway, such as tumor necrosis factor-alpha (TNF-α), caspase 8, and caspase 3 (Wu et al., 2005). *Trichinella spiralis* can induce apoptosis in HCC, because its infection has similar regulatory mechanisms to cancer cell apoptosis signals and it represents a promising approach to overcoming this cancer.

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Lung cancer

Among all malignant cancers worldwide, lung cancer has the highest mortality rate in humans (Bade and Cruz, 2020). Numerous factors, including population aging, smoking, and environmental pollution, have contributed to an increase in the mortality rate due to lung cancer in recent years (Rudin et al., 2021). Unfortunately, lung cancer is mostly identified at late stages, and the survival rate is less than 15% in 5 years. Due to the quick multiplication time in small cell lung cancer (SCLC), lung cancer has a poor prognosis (de Groot et al., 2018; Barta et al., 2019; Schabath and Cote, 2019; Thandra et al., 2021). Chemotherapy is the primary therapeutic option for advanced SCLCs but has significant side effects, including an increased risk of cancer recurrence (Yang et al., 2019; Oronsky et al., 2022). Contrarily, biological therapy is regarded as a secure and effective therapeutic approach. As a result, numerous experimental studies have been carried out to investigate how biological therapy can inhibit the growth of cancers, including those that examine the antineoplastic properties of parasites. According to numerous studies, *T. spiralis has two different types of antineoplastic mechanism*s. First, *T. spiralis* may cause an immunized response in the host by parasitizing tumor antigens of cancer cells. Second, *T. spiralis* may contain substances that directly start the apoptosis of cancer cells (Liao et al., 2018). *T. spiralis* could cause cell apoptosis through mitochondrial apoptosis pathways by first activating caspase-9 and then caspase-3 (Yu et al., 2014). The expression of pro-apoptosis genes like *BAX*, *Cyt-C*, *Apaf-1*, *caspase-9*, and *caspase-3* may be upregulated by ESPs, whereas the expression of anti-apoptosis genes *Bcl-2* and *Livin* may be downregulated (Bruschi et al., 2022). Therefore, it could be concluded that ESPs can activate mitochondria to release high levels of Cyt-C into the cytoplasm (Akl et al., 2014). The polymerization caused by Cytochrome C (Cyt-C) with Apoptotic protease activating factor-1 (Apaf-1) and procaspase-9 may further stimulate caspase-9 and caspase-3, which would then cut substrate proteins in the cell (Martínez-Lostao et al., 2015). The ESPs may also prevent the anti-apoptosis protein Livin from performing its apoptosis regulation functions on the cascade reaction, which would ultimately influence apoptosis in H446 cells, a small cell lung cancer cell line (Luo et al., 2017). As a result, *T. spiralis* Muscle larva (ML) ESPs trigger intrinsic mitochondrial pathways, which in turn cause apoptosis in H446 SCLC cells. In conclusion, it was found that *T. spiralis* ML ESPs may prevent human H446 SCLC cells from proliferating and trigger their apoptosis by activating mitochondrial apoptosis pathways.

Melanoma

The most aggressive type of skin cancer is melanoma in humans and animals (Miller and Mihm Jr, 2006). Because this tumor is largely resistant to conventional chemotherapy, patients with advanced disease have a poor prognosis (Garbe and Leiter, 2009; Schadendorf et al., 2018). Finding new therapeutic strategies for the treatment of melanoma could be a valuable subject for research to find substances that can affect the apoptotic process of the disease (Schadendorf et al., 2015; Domingues et al., 2018; O'Neill and Scoggins, 2019). All three stages of the T. *spiralis* life cycle appear to contain elements that can control malignancy based on a few studies currently available in this field. *Trichinella spiralis* can inhibit the growth of B16 melanoma by the action of ES L1 antigens (a component unique to the chronic phase of this infection, Kang et al., 2013). Studies conducted *in vitro* showed that ES L1 antigens affect B16 melanoma cells that are both anti-survival and pro-apoptotic (Vasilev et al., 2015).

CONCLUSION

Today, the knowledge of *T. spirals'* role in antitumor therapy has greatly improved due to advancements in research on the relationships between the organism and tumors. Antigens derived from parasites may be helpful in cancer immunotherapy in humans and animals. Studies conducted *in vitro* showed that *T. spiralis* antigens affect different cancer cells in hepatocellular carcinoma, lung cancer, and melanoma by activating mitochondrial apoptosis pathways. Cellular immune function, mediated by Th1 cells, suppresses malignant cell proliferation and angiogenesis. Clinical trials have not provided compelling evidence linking *T. spiralis* to the prevention or treatment of tumors. Future studies should focus on the purification of parasite antigens and their use for wider-scale trials in animal models.

DECLARATIONS

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Authors' contribution

Soheil Sadr was the principal author who directed and prepared the review paper. Zahra Yousefsani, Pouria Ahmadi Simab, Ahad Jafari Rahbar Alizadeh, and Narges Lotfalizadeh participated in the preparation of the final version of the manuscript. Hassan Borji participated as a supervisor and assisted in preparing and proofreading of the manuscript. All authors have read and approved the final version of the manuscript for publication in the present journal.

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