2023, Scienceline Publication
World's Veterinary Journal
World Vet J, 13(4): 606-616, December 25, 2023
ISSN 2322-4568

DOI: https://dx.doi.org/10.54203/scil.2023.wvj65

Using Helminths to Fight Cancer: An Innovative Approach

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REVIEW ARTICLE
pii: S232245682300065-13
Received: 03 September 2023
Accepted: 29 October 2023

ABSTRACT

As an alternative treatment in cancer therapy, there has been a growing interest in using helminths, such as *Trichinella spiralis* (*T. spiralis*), *Echinococcus granulosus* (*E. granulosus*), *Toxocara canis* (*T. canis*), and *Taenia solium* (*T. solium*). This study aimed to investigate the antigens and mechanisms that contribute to the anticancer properties of helminths, providing insights into how helminths may be used as a new and innovative treatment modality for cancer. The current review analyzed preclinical and clinical studies published between 2000 and 2023. The present study sought to obtain information on helminths, such as *E. granulosus*, *T. spiralis*, *T. canis*, and *T. solium*, to treat cancers of the breast, pancreas, melanoma, and leukemia by exploring databases, such as PubMed, Google Scholar, and Scopus. Studies focusing on helminth therapy against particular cancer types for *in vitro* and animal models were included. Several studies have shown the possibility of inhibiting breast, colon, melanoma, and leukemia tumor growth, inducing apoptosis, and modulating the tumor microenvironment with *E. granulosus*, *T. spiralis*, *T. canis*, and *T. solium* based on *in vitro* and animal models studies. Some studies have indicated that helminth therapy can improve survival rates, reduce tumor growth, and stimulate the immune system in cancer patients. A potential improvement in treatment outcomes can be used for combination therapies, such as antigen selection, immune profiling, and individualized approaches based on helminth therapy. Helminth therapy is an additional option for cancer treatment, emphasizing *T. spiralis*, *E. granulosus*, *T. canis*, and *T. solium*. These helminth antigens could modulate immune responses and directly cause cytotoxicity in cancer cells.

Keywords: Cancer, *Echinococcus granulosus*, *Taenia solium*, *Toxocara canis*, *Trichinella spiralis*

INTRODUCTION

Modern medicine must deal with the daunting challenge of treating cancer, a disease that affects millions of people worldwide. Researchers are still seeking more efficient and less harmful cancer treatment options despite impressive advances in conventional methods such as radiation therapy and chemotherapy (Mansouri et al., 2021; Hajjafari et al., 2022; Saeed et al., 2022). Alternative approaches to dealing with this complicated condition have recently gained considerable popularity (Sadr et al., 2023a). One promising approach is to utilize parasitic worms, which have co-evolved with humans for thousands of years (Asouli et al., 2023; Sadr et al., 2023b).

Flukes, roundworms, and tapeworms are all examples of helminths (Lotfalizadeh et al., 2022). Historically, most of them are responsible for human diseases, but scientific evidence in recent years indicates that they may also provide therapeutic benefits, especially for cancer treatment (Oikonomopoulou et al., 2014; Scholte et al., 2018). Parasitic helminths such as *Trichinella spiralis* (*T. spiralis*), *Echinococcus granulosus* (*E. granulosus*), *Toxocara canis* (*T. canis*), and *Taenia solium* (*T. solium*) have offered a novel perspective on cancer treatment due to their antigen similarity with cancer (Ditgen et al., 2014; Asghari et al., 2022). It has been discovered that some of these molecules can modulate the immune system at a fundamental level, which is a critical factor in the development and progression of cancer (Callejas et al., 2019).

To avoid the host's immune response, helminths can induce an immune state of immunomodulation, achieved by switching from a pro-inflammatory and inflammatory environment to a regulatory one, thus evading the host's defense (Bruschi and Chiumiento, 2012; Bruschi et al., 2022). Several studies have demonstrated that helminth-induced immune modulation has profound implications for cancer, suppressing tumor-promoting inflammation, enhancing antitumor immune responses, and restoring immune balance in tumor microenvironments (Guan et al., 2019; Raisnia et al., 2022).

To cite this paper: Ameli N, Masoumi A, Kerachi M, Sheidaeimehneh N, Khavidaki NL, and Zamanian M (2023). Using Helminths to Fight Cancer: An Innovative Approach. *World Vet. J.*, 13 (4): 606-616. DOI: https://dx.doi.org/10.54203/scil.2023.wvj65

There is significant evidence that helminth infestation improves survival rates, inhibits tumor growth, and minimizes metastasis in animal infestation models (Daneshpour et al., 2016; Berriel et al., 2021). Some preliminary clinical trials conducted with helminths showed promising results, such as tumor regression, immune activation, and improved overall survival in patients treated with helminths (Aref et al., 2013; Daneshpour et al., 2019).

While helminth therapy has many benefits, it has many challenges as well. The development of protocols must consider several important factors, including ethical considerations, safety concerns, and standardization. To identify patient selection criteria and optimize treatment strategies, more research is necessary to identify the individuals' responses to helminth therapy. The present study aimed to understand the intricate relationship between helminths and cancer by analyzing how helminths interact with the immune system. By doing so, researchers can better understand how helminths exert their anticancer properties.

METHODOLOGY

This systematic review aimed to investigate the potential therapeutic benefits of *T. spiralis*, *E. granulosus*, *T. canis*, and *T. solium* in treating breast, pancreatic, leukemia, and melanoma cancers by applying an integrated methodology. The studies published between 2000 and 2023 were reviewed for the present review.

To begin the review process, several databases were searched in the current study, including PubMed, Embase, Scopus, and Web of Science. Several relevant keywords and their variations were included to ensure comprehensive coverage. These keywords include "helminths," "*Echinococcus granulosus*," "*Trichinella spiralis*," "breast cancer," "pancreatic cancer," "leukemia", and "melanoma".

In the scope of this systematic review, the inclusion criteria included studies that employed an integrated methodology. These studies explored the therapeutic potential of *T. spiralis*, *E. granulosus*, *T. canis*, and *T. solium* in various cancers, specifically breast, pancreatic, leukemia, and melanoma. As a result, exclusion criteria include studies that do not pertain to the therapeutic aspects of these helminths in cancer, those that do not use an integrated methodology, publications that do not coincide with the specified timeframe, studies that are not focused on cancer, non-clinical or non-preclinical research, and studies that do not follow a primary objective to assess whether helminth therapy can be beneficial for cancer. English-language publications are the only ones considered, whether performed *in vitro*, *in vivo*, or in clinical tests. The current study selected 43 studies out of 427 studies published between 2000 and 2023 to ensure that contemporary research is represented.

ANTICANCER PROPERTIES

Animals and humans both suffer from helminth infections as parasitic organisms. A variety of parasites live in the animal and human body, including roundworms (nematodes), tapeworms (cestodes), and flukes (trematodes). Recent research shows that helminths' Excretory-Secretory Proteins (ESP) may have therapeutic potential against cancer despite their mysterious anticancer properties (Kang et al., 2013; Liao et al., 2018).

Helminths anticancer properties must be better understood by unraveling the mechanisms underlying them. Helminth has multifaceted strategies to interact with the immune system, such as creating an environment that is uniquely anticancer. By activating the immune system, helminths can modify the host's immune response (Ding et al., 2020; Hu et al., 2021). It is important to note that immunomodulation plays a significant role in suppressing tumor growth and metastasis (Vasilev et al., 2015).

Bioactive molecules produced by helminths may directly target cancer cells or may be influenced by their microenvironment (Gutierrez-Millan et al., 2021). Various molecules, including glycoproteins and ESP, have anticancer properties (Osinaga, 2007; Bahadory et al., 2022). When ES proteins are secreted, apoptosis can be induced by helminth-derived proteins in animal-induced cancer cells, and angiogenesis and metastasis can be inhibited (Mu et al., 2021). Excretory and secretory proteins of helminths possess exceptional immunomodulatory characteristics and a direct effect on cancerous tissues (Murphy et al., 2020). By creating anti-inflammatory and immune-regulating environments, they have adapted tactics to undermine the host's immune system reaction and counteract inflammation that reduces tumor development (Kahl et al., 2018). The tumor microenvironment influences the immune system by interacting with various regulatory molecules and immunological cells like CD8+ T cells and natural killer (NK) cells (Sotillo et al., 2020).

Helminths can include enhancing the activity of NK cells by stimulating a type 2 immune response (Nutman, 2015). Moreover, immune modulation by helminths can trigger the production of anti-inflammatory cytokines and the recruitment of regulatory T cells (Tregs), which suppress excessive immune responses (White et al., 2020). Helminths can inhibit tumor growth by dampening chronic inflammation, which is a known risk factor for cancer. In addition to controlling chronic inflammation, helminths help regulate the immune system by inhibiting tumor growth (Vennervald and Polman, 2009).

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Through the interaction of helminth-derived molecules with host immune cells, the immune system alters the function of immune cells, produces cytokines, and creates immune signaling pathways in response to inflammation (Elliott and Weinstock, 2012; Motran et al., 2018; Maizels, 2020). To harness the anticancer potential of helminths effectively, it is imperative that researchers fully comprehend the details of immunomodulation. Helminths exert their anticancer effects by modulating the immune system and directly targeting cancer cells (Reens et al., 2021; Asghari et al., 2022; Lee et al., 2023). Helminth's capabilities could be harnessed to enhance or complement anticancer therapies.

IMMUNE SYSTEM MODULATION

How helminths interact with the immune system

Interfacing with the host's immune system can be accomplished by helminths in several different ways. In addition to direct interactions with immune cells, immunomodulatory molecules are secreted, and immune signaling pathways are modulated during these interactions (Hewitson et al., 2009; Zheng et al., 2020). Helminths influence the immune system in a variety of ways, including pattern recognition receptors (PRRs). Lipids, glycoproteins, and other molecules derived from helminths can bind to PRRs within immune cells (Abou-El-Naga and Mogahed, 2022). Immune responses are activated by PRRs when they recognize pathogen-associated patterns (Tsubokawa, 2023). Immune cells become activated after helminth molecules bind to PRRs, which affects downstream processes.

Helminths can modify Antigen-Presenting Cells (APCs) such as dendritic cells and macrophages, also modifying how antigens are presented to T cells (Harn et al., 2009; Nutman, 2015). Consequently, distinct immunological responses that are less favorable to tumor growth can be developed.

Helminths influence immune responses by influencing cytokines, which are significant for signaling (Kaur and Ghorai, 2022). Parasites can induce anti-inflammatory cytokines, such as IL-10 and TGF-β, while suppressing pro-inflammatory cytokines, like IL-6 and TNF-α (Yeo et al., 2021; Silva et al., 2023). This cytokine modulation contributes to an immunosuppressive environment. By recruiting Tregs and promoting an anti-inflammatory environment, helminths may facilitate immune tolerance (Ryan et al., 2020).

Some helminths are capable of directly interacting with immune cells, including eosinophils, macrophages, and Natural Killer (NK) cells (Maggi et al., 2020; Zhou et al., 2020; Varadé et al., 2021). This results in their activation and recruitment to infection or inflammation sites. Antitumor action can be exerted by activated immune cells by directly interacting with tumor cells or enhancing immune surveillance (Gong et al., 2020; Peng and Fadeel, 2022).

Impact of helminth-induced immunomodulation

Aside from altering the immune system by activating DCs and T cells, helminth infections have profound implications for cancer development and progression. Helminths have the capability to alleviate chronic inflammation associated with the growth of cancer (Arabpour et al., 2021). By reducing pro-inflammatory cytokine production in the immune system and increasing anti-inflammatory cytokine production, helminths prevent tumor development (Shi et al., 2022). Helminth infection increases the activity of immune cells, such as cytotoxic T cells and NK cells, that promote the immune system's ability to fight cancer (Dyck and Mills, 2017; Roe, 2022). The cancerous cells can be detected and destroyed by these immune cells. Activating the immune system induced by helminths can improve its ability to identify and eliminate cancerous lesions by enhancing their effector activities (Maizels and McSorley, 2016; Callejas et al., 2018). Helminths appear to influence angiogenesis, which involves the formation of blood vessels that supply oxygen and nutrients to tumors (Williams et al., 2016). Helminths prevent angiogenesis by inhibiting angiogenic factor secretion, which prevents tumor development and metastasis (Dehne et al., 2017). Further, helminth-induced immunomodulation can restrict the invasion of cancer cells and their migration, thereby suppressing metastatic spread (Chakraborty et al., 2023).

T cells in helminth therapy

Regulatory T cells (Tregs) play a crucial role in maintaining immune homeostasis and limiting excessive immune responses. In helminth infections and treatments, Tregs play an important role in modulating immune responses (Babu and Nutman, 2019). Immunosuppressive properties can be induced by helminths, which can expand and activate Tregs (McManus and Maizels, 2023). To suppress immune responses against tumors, Tregs suppress the function of cytotoxic T cells and natural killer cells by blocking their operations. As a result, Treg suppression diminishes the immune responses against tumors (Belkaid and Tarbell, 2009).

There is much to learn about Tregs and their role in cancer helminth therapy. Through their ability to reduce inflammation and minimize immune-mediated damage, helminths facilitate the formation of Tregs and support antitumor immunity (Toomer and Chen, 2014). Previously, studies have been conducted on the interaction between helminths, Tregs, and antitumor immune responses (Grazia Roncarolo et al., 2006; Li et al., 2015). Determining how helminths modulate Treg activity is imperative to optimize helminth-based therapeutic strategies (Vahidian et al., 2019; Figure 1).

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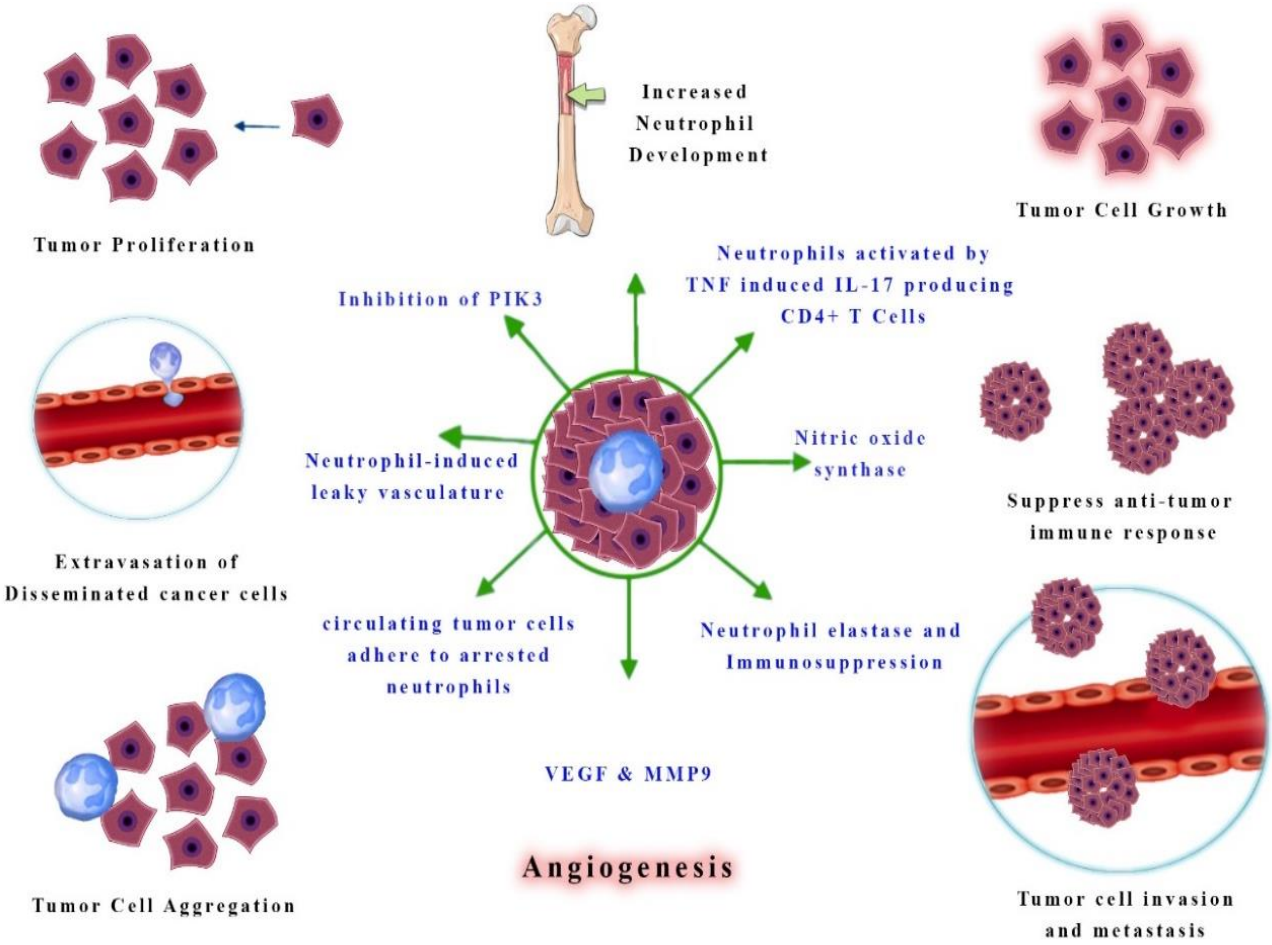

Figure 1. The mechanisms of helminths interact with the immune system. Helminth-induced immunomodulation on cancer development and progression, PIK3: Phosphoinositide 3-kinases, VEGF: Vascular endothelial growth factor, TNF: Tumor necrosis factor, IL: Interleukin, MMP9: Matrix metalloproteinase 9, CD 4+: Cluster of differentiation 4

HELMINTH AND CANCER TREATMENT

Echinococcus granulosus

Echinococcus granulosus is a tapeworm primarily found in canids such as dogs and wolves, and herbivores such as sheep and cattle serve as intermediate hosts (Devadharshini et al., 2022; Shams et al., 2022). To survive, *E. granulosus* goes through various stages in its life cycle. During adulthood, worms live in definitive hosts' small intestines, producing eggs expelled in their feces (Heidari et al., 2019). Infected canids pass the tapeworm eggs in their feces, which are then eaten by intermediate hosts (usually herbivores) where they develop into cysts, which are then consumed by the canids, releasing the tapeworm's adult stage into their intestines (Tamarozzi et al., 2020).

Intermediate hosts swallow eggs and hatch them in the small intestine, releasing oncospheres. The oncospheres enter the bloodstream through the intestinal wall, which causes a hydatid cyst to form in an organ like the liver or lungs (Pal et al., 2022; Thompson, 2023). The protoscoleces that develop within hydatid cysts can produce adult worms if eaten by the appropriate definitive host (Borhani et al., 2021).

Several antigens obtained from *E. granulosus* have been investigated as possible cancer treatment options (Chookami et al., 2016; Sharafi et al., 2016; Asouli et al., 2023). Numerous studies have been conducted on the immunogenicity of antigen B (AgB) and its ability to induce immune reactions in response to tumor cells (Darani and Yousefi, 2012). Evidence shows that the multi-subunit antigen AgB triggers both humoral and cellular immune responses (Rigano et al., 2007). Cancer cells can be induced to undergo apoptosis by AgB, the growth of tumors can be slowed down, and immune cells attack tumors more effectively by AgB (Noya et al., 2013; Zheng, 2013). Antigen 1 (Ag1) and Antigen 5 (Ag5) from *E. granulosus* have also been investigated concerning their anticancer capabilities (Daneshpour et al., 2016; Darani et al., 2016; Sharafi et al., 2018; Bo et al., 2020).

Trichinella spiralis

Several types of mammals carry *T. spiralis*, including carnivorous and omnivorous mammals such as humans (Zarlenga et al., 2020). There are different stages in the life cycle of *T. spiralis*. Adult worms live in the small intestine, where they reproduce sexually and produce larvae (Tang et al., 2022). By injecting the larvae into the bloodstream, the

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larvae penetrate the intestinal wall and migrate to different tissues, including skeletal muscles. As the larvae penetrate muscle tissue, they get encapsulated, producing nurse cells (Barlow et al., 2021). When an animal feeds on infected muscle tissue, larvae are released, which can grow into adult parasites.

Many antigens derived from *T. spiralis* benefit cancer treatment (Eissa et al., 2016; Bruschi et al., 2022; Yousefi et al., 2023). Glycoprotein *T. spiralis* is known to possess anticancer properties based on preclinical trials. Several studies have shown that *T. spiralis* triggers apoptosis in tumor cells, prevents tumor growth, and enhances immune reactions against tumors (Callejas et al., 2018; Ding et al., 2021; Sadr et al., 2023c). It has also been found that TSL-ES, an excretory-secretory antigen of muscle larvae of *T. spiralis*, suppresses tumor proliferation by modulating tumor microenvironments (Ding et al., 2021; Ding et al., 2022). The ability of *T. spiralis* antigens to activate dendritic cells and trigger immune responses against tumor cells has also been explored (Saad and Ghanem, 2020; Bruschi et al., 2022) (Figure 2). The dendritic cells can then present tumor-associated antigens to T cells, ultimately enhancing the immune response against tumor cells and reducing the risk of malignancies.

Toxocara canis

Toxocara canis is an intestinal parasite found mainly in dogs (Macpherson, 2013). However, it can also infect humans, leading to the development of a disease known as human toxocariasis (Jahanmahin and Borji, 2023). This occurs when someone accidentally ingests the parasite's eggs through contact with contaminated soil or objects. *T. canis* has been investigated for its potential anticancer effects (Oikonomopoulou et al., 2013; Jahanmahin and Borji, 2023;). Despite *T. canis* infections most commonly affecting the liver, lungs, and eyes in humans, Garn et al. (2021) indicated that exposure to *T. canis* antigens may reduce the risk of certain types of cancer, such as breast and colon cancers (Garn et al., 2021). There is still uncertainty about the mechanisms underlying these effects, but it is believed that they include multifaceted interactions between *Toxocara*'s antigens and the host's immune system. According to studies, *Toxocara* antigens have the potential to modulate the immune reaction, resulting in an increase in immune cell activity, such as macrophages, DCs, and NK cells. Macrophages and NK cells can recognize and target cancer cells, leading to their demise. Aside from the stimulation of chemokines and cytokines, *Toxocara* antigens also contribute to the regulation of the immune response and the development of tumors. The infection of *Toxocara* may also trigger the production of T2 immune responses related to the production of specific antibodies and cytokines that inhibit tumor growth (Menon et al., 2021). Research is needed to understand how *Toxocara* antigens generate anticancer effects and determine their effectiveness as cancer therapeutics.

Recent studies reported the effect of *T. gondii* and *T. canis* egg antigens on transplanted WEHI-164 fibrosarcoma in BALB/c mice (Darani et al., 2009; Darani and Yousefi, 2012). Researchers found that parasites *T. gondii* and eggs of *T. canis* inhibit tumor proliferation in the fibrosarcoma mouse model. However, the underlying mechanisms responsible for these effects require further investigation.

Based on the *T. canis* ESP, Bahadory et al. (2022) assessed the potential anticancer activity of this parasite (Bahadory et al., 2022). The expression of cancer-related genes and tumor cell viability was studied in liver and gastrointestinal cancer cell lines treated with synthesized peptide components obtained from *T. canis*. More than 32 µg/ml concentrations showed efficacy in other cancer cell lines.

Taenia solium

According to studies, certain constituents of *Taenia solium* can potentially interact with cancer cells and possibly exert anticancer effects (Arora et al., 2020; García-Gutiérrez et al., 2020; Plata and Castañeda, 2020). Schcolnik-Cabrera 2020 evaluated the anticancer activities of recombinant *T. solium* calreticulin (rTsCRT) by treating tumor cells at various concentrations (Schcolnik-Cabrera et al., 2020). Tests were also undertaken by employing cancer cell lines with rTsCRT and 5-fluorouracil, a chemotherapy medication. It was demonstrated that rTsCRT acted as an antitumor agent dose-dependently in SKOV3 and MCF7 cell lines. The study found that cells had lower viability and colony-forming ability in combination with 5-fluorouracil. In addition, cancer stem-like cells showed greater sensitivity to the treatment of rTsCRT. In addition, rTsCRT's involvement in scavenger receptor interactions profoundly affected its antitumor properties since blocking these receptors reversed rTsCRT's viability reduction characteristics. The rTsCRT may be beneficial as a therapy for breast and ovary cancers because it interacts with scavenger receptors.

CHALLENGES AND FUTURE DIRECTIONS

Helminth therapy can be a valuable treatment option for cancer, but several challenges and limitations must be addressed to implement it in clinical settings successfully. Future advancements in the field can be facilitated by improving treatment methods based on helminths and surmounting these obstacles.

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CURRENT LIMITATIONS AND CHALLENGES

As promising as helminth therapy has been in preclinical studies and limited clinical trials, safety concerns remain paramount. When administered live helminths, individuals with impaired immune systems may experience uncontrolled infections, migration to unintended organs, or adverse reactions (Sobotková et al., 2019). Applying comprehensive evaluations and maintaining standardized processes should make helminth therapy safe (Weinstock and Elliott, 2009).

Ethical questions must be addressed if individuals are intentionally infected with parasitic organisms to undergo helminth therapy (Lukeš et al., 2014). The debate regarding the deliberate administration of parasites into patients is going on, bearing in mind possible therapeutic advantages and ethical considerations. A framework and guidelines that protect patient well-being and autonomy are imperative to navigate these complicated issues (Sobotková et al., 2019).

No standardized treatment protocol exists for helminth therapy, including terms such as duration of therapy, dosage, and timing (Cheng et al., 2015). Guidelines must be designed to ensure consistent and reproducible helminth administration, monitoring, and patient follow-up (Fleming and Weinstock, 2015).

Different types of cancer, stages, and genetic profiles exist among individuals with cancer, depending on the type and location of the disease (Zheng, 2013). There may be some individual differences in response to helminth therapy, which necessitates the identification of patient selection criteria as well as predictive biomarkers for optimizing treatment outcomes. Developing personalized approaches to helminth-based cancer therapy requires knowledge of the factors responsible for heterogeneity in response (Douglas et al., 2021).

ONGOING RESEARCH AND POTENTIAL IMPROVEMENTS

Researchers are currently investigating the development of antigens derived from helminths capable of delivering robust anticancer activity with the least adverse effects possible (Muzzarelli, 2010; Noya et al., 2013). Researchers need to aim to formulate standardized and controlled antigen compounds by pinpointing and isolating essential immunogenic elements. Using recombinant DNA technology facilitates the preparation of helminth antigens at high levels in a reproducible and reliable way. By manipulating antigen structure and composition precisely, improving their effectiveness and safety may be possible (Bolhassani et al., 2011). Some of these properties are increasing immunity, reducing side effects, or improving tissue targeting. Additionally, engineering recombinant antigens permit various antigen fusions and modifications for maximum anticancer efficacy (Saylor et al., 2020). It is possible to increase the potency of helminth therapy when combined with immunotherapy adjuvants or other cancer treatments (Li et al., 2019). Helminth antigens stimulate an immune response, strengthening their anticancer effects when used with immune adjuvants (Liu et al., 2019). Helminth therapy may synergize with traditional treatments, such as chemotherapy and immunotherapy, and improve the overall efficiency of such therapies (Lim, 2015).

Combination therapies

It may be possible to enhance treatment results when helminth therapy is used alongside conventional cancer treatments, for example, radiotherapy, chemotherapy, and immunotherapy. Treatments that target the immune system, such as adoptive cell therapies or immune checkpoint inhibitors, may be boosted by immune modulation caused by helminths (Elsegood et al., 2017; Thuru et al., 2022). In many ways, helminth therapy can improve the immune response against tumors by enhancing the immune reaction triggered by regulatory and anti-inflammatory environments induced by helminth therapy (Crinier et al., 2019). Helminth therapy might make cancerous cells more susceptible to chemotherapy, making them more vulnerable to its cytotoxic effects. By modulating the tumor microenvironment and strengthening immune responses to chemotherapy, helminth therapy can improve chemotherapy efficacy and minimize the duration and dosage of treatment (Wei et al., 2021). Colliding helminth therapy with radiation therapy can sensitize tumor cells more prone to radiation. Helminths may modulate the immune system, and the tumor microenvironment may be altered, leading to a better tumor response to radiation.

CONCLUSION

Helminth therapy is proving to be a promising new treatment frontier for cancer, offering improved outcomes, fewer side effects, and a personalized approach. Using helminth therapy in combination with traditional cancer treatments may lead to better treatment outcomes. As a result of coupling helminth therapy's unique mechanism of action with chemotherapy, radiotherapy, or immunotherapy, more complete and efficient cancer treatment plans can be developed. Combining chemotherapy with radiotherapy for precision or pairing immunotherapy with radiation therapy for immunomodulation can achieve more comprehensive and highly successful treatments for breast, colon, lung, and melanoma cancers. Moreover, antigen selection and immune profiling allow helminth-based treatments to be customized individually to the patient's requirements, ensuring optimized treatment responses. Future advancements in helminth

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therapy can be achieved by designing creative therapies that use helminths and gaining a better understanding of their mechanisms.

DECLARATIONS

Ethical approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Authors' contributions

The conceptualization of the study was led by Melika Zamanian, with all authors contributing to the methodology. Formal analysis and investigation were carried out by all authors, and the original draft of the manuscript was collectively prepared by them. Additionally, all authors participated in the review and editing process, with Melika Zamanian overseeing the project as the supervisor. All authors checked and approved the final version of the manuscript for publication in the present journal.

Funding

No funding was received for conducting this study.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no conflict of interest.

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To cite this paper: Ameli N, Masoumi A, Kerachi M, Sheidaeimehneh N, Khavidaki NL, and Zamanian M (2023). Using Helminths to Fight Cancer: An Innovative Approach. *World Vet. J.*, 13 (4): 606-616. DOI: https://dx.doi.org/10.54203/scil.2023.wvj65

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To cite this paper: Ameli N, Masoumi A, Kerachi M, Sheidaeimehneh N, Khavidaki NL, and Zamanian M (2023). Using Helminths to Fight Cancer: An Innovative Approach. *World Vet. J.*, 13 (4): 606-616. DOI: https://dx.doi.org/10.54203/scil.2023.wvj65

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To cite this paper: Ameli N, Masoumi A, Kerachi M, Sheidaeimehneh N, Khavidaki NL, and Zamanian M (2023). Using Helminths to Fight Cancer: An Innovative Approach. *World Vet. J.*, 13 (4): 606-616. DOI: https://dx.doi.org/10.54203/scil.2023.wvj65

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