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Can Parasites be Useful?

Parazitler Yararlı Olabilir mi?

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ABSTRACT

Parasites are commonly associated with harm, but they also have beneficial aspects that are still being discovered. It is important to acknowledge both the harmful and beneficial aspects of parasites. They have been found to have positive effects on non-healing wounds, surgical wounds, obesity, glucose metabolism disorders, nerve repair, cancer treatments, and fertility. Research has shown that helminths, protozoa, and arthropods have the ability to correct, prevent, and cure certain disorders through the use of the parasite itself, its molecules, or even its eggs. This article includes studies on the beneficial aspects of parasites. However, further research is needed to fully understand the mechanisms by which parasites stimulate or affect the immune system and how they can be used therapeutically.
Keywords: Benefits of parasites, maggot therapy, hirudo therapy, parasitomimetics, ascarosides

ÖZ

Parazitler genellikle zararlı yönleri ile bilinen canlılardır. Parazitlerin zararlarının yanında yararlı yönleri de keşfedilmiş ve halen günümüzde keşfedilecek birçok yararlı yönü bulunmaktadır. İyileşmeyen yaralarda, cerrahi operasyon sonrası yaralarda, obezite ve glikoz metabolizması bozukluklarında, sinir onarımında, kanser tedavilerinde hatta doğurganlık üzerine yararlı etkileri olduğu bildirilmiştir. Helmintlerin, protozoonların ve artropodların, parazitin kendisi ya da salgıladığı molekülleri hatta yumurtaları ile belirli bozuklukları düzeltebildiği, engelleyebildiği ve iyileştirebildiği kanıtlanmıştır. Bu yazıda parazitlerin yararlı yönleri ile alakalı çalışmalara yer verilmiştir. Parazitlerin birçoğunun bağışıklık sistemini uyarması ya da etkilemesi ile yarar sağladığı mekanizmaları anlamak ve terapötik amaçla kullanılabilmesini sağlamak için çok daha fazla çalışmaya ihtiyaç vardır.
Anahtar Kelimeler: Parazitlerin faydaları, maggot terapi, hirudo terapi, parazitomimetikler, askarozitler

INTRODUCTION

The term “Parasite” is derived from the Latin words “para” (beside) and “cytos” (food). It refers to a living being that lives off another organism, known as the host. Parasitism is the phenomenon of a living organism living on or in another living organism, temporarily or permanently, to its detriment (1).

However, recent studies have shown that parasites can have both positive and negative effects on their hosts. Research has demonstrated that parasites, including their eggs, developmental forms, and molecules, can provide benefits by affecting certain systems or triggering various mechanisms in humans and animals (2).

While the immune system can expel microorganisms that invade the body, parasites must evolve to maintain their symbiotic relationship with their hosts. Parasites can manipulate the host’s immune system by producing immunomodulatory molecules. They can control specific host immunity and affect the entire immune system (2).

As the host develops its immune system against the parasite, the parasite develops mechanisms to evade immunity. The regulation of host immunity by parasites has been a long-standing research topic. The positive effects of helminths, protozoa, and arthropods have been discussed based on species and grouped according to treatment methods with successful results (2,3).

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Türkiye PARAZİTOLOJİ Dergisi

Maggot Therapy

Myiasis, which originates from the Latin word "Myia" fly, is the name given to the disease caused by the feeding some fly larvae on the tissues of humans and animals (4).

Myiasis is a prevalent disease worldwide. The adult flies responsible for this disease are usually found in Türkiye from April to September. Myiasis is more prevalent during the summer months in areas where sheep and goats are raised (4).

Although myiasis larvae can have harmful effects, they are sometimes used in forensic medicine and wound treatment. The use of live fly larvae to treat wounds is becoming increasingly popular worldwide. These larvae develop in environments where decay and putrefaction occur, and they can be necessary in cases where wound healing is crucial due to microorganisms that are resistant to antibiotics. The treatment is known by several names, such as larval therapy, maggot therapy, biosurgery, and maggot debridement therapy (MDT) (5).

Maggot therapy is a controlled myiasis in open wounds to utilise the positive effects of larvae on necrotic tissue without damaging the intact tissue (6).

Fly larvae suitable for maggot therapy are typically found in the Calliphoridae family (6). The most commonly used species is *Lucilia sericata* (syn. *Phaenicia sericata*). *Lucilia sericata* is preferred due to its ability to feed on dead tissue on the surface of living tissue (7,8).

Cage dressings are the preferred method for maggot therapy (9). Another method, Biobag, has also been used in Maggot therapy applications (10,11).

Maggot therapy is commonly used to treat infected wounds that are unresponsive to treatment. It can also help heal ulcers caused by various factors such as pressure, venous stagnation, nerve disease, surgical operations, trauma, burns, cellulitis, bone marrow inflammation, mastoiditis, thalassemia, polycythemia, Burger disease, necrotic tumors, and crusted or incompletely healed wounds (12).

MDT has found a new role in treating diseases caused by many Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus*, *Pseudomonas aeruginos*a, and methicillin-resistant *Staphylococcus*, due to the increasing incidence of drug resistance in recent years (11).

Kerridge et al. (13) incubated 100 sterile *L. sericata* larvae in 10 mL of bidistilled water overnight. The liquid was collected, centrifuged, filtered, and lyophilised. The resulting secretion material was dried, frozen, and resuspended in bidistilled water. The authors reported that this material exhibited antibacterial effects against MRSA (Methicillin Resistant *Staphylococcus aureus*), *Streptococcus pyogenes*, and *Pseudomonas aeruginosa* under *in vitro* conditions.

Jaklič et al. (14) demonstrated that *in vitro* conditions, larval secretions of *L. sericata* possess antibacterial activity against *S. aureus*, *E. coli*, and *P. aeruginosa*.

Harris et al. (15) discovered that larval secretions containing the enzyme chymotrypsin can inhibits *Staphylococcus epidermidis* biofilm. Additionally, maggot secretions can break down established biofilm and prevent biofilm its formation on both abiotic surfaces such as polyethylene, stainless steel, and titanium, as well as on biotic surfaces.

Bohova et al. (16) conducted a study which found that worm secretions effectively reduced biofilm formation of *Enterobacter cloacae* and *S. aureus*, but not against *Proteus mirabilis*.

Clinical studies conducted in a laboratory have shown that larval secretions promote the migration of fibroblasts and keratinocytes, increase angiogenesis and enhance the migration of vascular endothelial cells (11).

Upon analysis the effect of maggot debridement treatment on antibiotic use, it was found that MDT has a synergistic impact on several antibiotics, including gentamicin, flucloxacillin and daptomycin at high concentrations, rather than inhibiting their antibacterial activity. Furthermore, an enhanced effect was observed when larval wastes and secretions were combined with ciprofloxacin (11).

The human complement system plays a crucial role in activating the inflammatory response to injury. However, inappropriate activation can cause severe tissue damage, as observed in chronic wounds that remain in the inflammatory healing phase. Studies have shown that larval secretions can inhibit pro-inflammatory responses in human neutrophils and monocytes without affecting the antimicrobial activities of phagocytes. The study found that inhibiting complement pathways, cytokines, and degrading complement proteins reduced all complement by up to 99.9% (17,18).

Hirudo (Leech) Treatment

"Leech" is derived from the Anglo-Saxon word "laece", which means doctor. The use of *Hirudo medicinalis* in treatments was described by Linnaeus in 1758 (19).

The medicinal leech *Hirudo medicinalis*, has been approved by the United States Food and Drug Administration as a prescription therapeutic material due to the many protease inhibitors found in its saliva. Molecular studies have revealed that there are at least three species of European medicinal leeches and leeches marketed as *H. medicinalis* are actually *Hirudo verbana*. These findings have prompted a review of decades of biomedical research on the organism and a reassessment of regulatory statutes, regulations, and protective measures (20).

Leeches have been used extensively worldwide in recent years. They have been particularly successful in plastic and reconstructive microsurgery in the UK and Ireland, where they are used to alleviate venous occlusion following flap surgery (21,22).

The Impact of *Trichuris* spp. Eggs on Autoimmune Diseases

Clinical trials have investigated the treatment of allergic rhinitis, multiple sclerosis (MS), ulcerative colitis, Crohn's disease, and inflammatory bowel disease through oral ingestion of the swine nematode *Trichuris suis* parasite eggs. These studies have identified beneficial aspects (23).

In 2010, a study was conducted in Finland to investigate the effectiveness of *T. suis* eggs in treating allergic rhinitis. Experimental studies have shown that they protect against allergic airway inflammation. In some observational studies, they have been associated with a reduced risk of atopy and alleviation of asthma symptoms. Treating allergic rhinitis with *Trichuris suis* eggs results in a significant clinical and systemic immunological response in humans. However, no therapeutic effect has been reported (23).

MS is more common in developed countries, but its prevalence is lower in areas where *Trichuris trichiura* carriage rates exceed 10%. Some studies suggest that this may be due to increased helminth exposure, which could have a protective effect against MS. Furthermore, research has shown that MS patients with helminth infections tend to have a milder disease activity and course than those without (24).

Ulcerative colitis is more common in developed Western countries but less prevalent in developing countries where helminth infections are more frequent. Individuals with helminth infections show a modified immunological response to antigens. In animal experiments, helminths have been shown to prevent or alleviate ulcerative colitis by stimulating regulatory T-cells and modulatory cytokines (25).

Helminths have been suggested to have potential benefits in reducing hyperreactive immune responses. This theory is supported by experimental findings that helminth eggs and live intestinal helminths protect against inflammatory bowel disease in mice and can even cure ongoing disease (25).

Similar to other inflammatory bowel diseases, Crohn's disease is less prevalent in less developed countries but more prevalent in developed countries. Exposure to helminths has been linked to a reduced immune response, which may help prevent or treat Crohn's disease (26).

Summers et al. (26) conducted a study on 29 patients with Crohn's disease who were orally administered 2500 live *T. suis* eggs every three weeks for 24 weeks. The study reported a success rate of approximately 80% at the end of 24 weeks. The treatment was found to be safe even for patients receiving multiple immunosuppressants, such as corticosteroids and azathioprine, without causing any side effects or complications.

The Benefical Effects of *Trichinella* spp.

Trichinella spiralis is a parasite that can survive in both adult and larval forms within two different cell environments in the same host. This immunomodulation ensures the survival of both the host and the parasite. The immune response is modulated by various cells from both the innate and adaptive divisions of immunity, including dendritic cells, T regulatory cells, and alternatively activated macrophages. The parasite can evade the immune system through several processes. Researchers are investigating molecules derived from parasites, including *Trichinella*, for their potential to treat immunopathology in animal models of various inflammatory and autoimmune human diseases. This includes components of their excretory-secretory products (27).

During trichinellosis, the immune system is stimulated by various molecules produced by the parasite. These molecules can be found in the cuticle or excretory-secretory products. The interaction between these molecules and the host's immune system can cause a shift in the immune response from an inflammatory to an anti-inflammatory type (28).

Trichinella-derived molecules have been shown to modify antigen-presenting cells, such as dendritic cells, and reduce adaptive immune responses (29).

Investigating how helminth parasites, such as *Trichinella*, modulate the immune system provides insights into the molecules involved in different parts, elements, and interactions within the immune system. These insights may be translated into future therapeutics. Currently, *Trichinella*-derived molecules, particularly excretory and secretory products, are the focus of intensive research aimed at discovering molecules to re-regulate the immune system in various immune dysregulations (28).

While the mechanism by which helminths treat osteoclastic bone destruction is not fully understood, helminths and helminth-derived products have shown promise in treating joint bone erosion in rheumatoid arthritis (30).

Trichinella spiralis infection or certain products secreted by its larvae in muscles have been found to inhibit bone erosion and osteogenesis in mice with collagen-induced arthritis (CIA) by inhibiting M1 monocyte/macrophage polarization and production. The study utilized mice infected with *T. spiralis* 14 days prior to the onset of CIA. The larvae were observed to reach the skeletal muscle 28 days after oral administration. Micro-computed tomography was used to visualise the mice after stimulation with CIA. The results showed severe bone erosions in CIA mice, which were not visible in the normal control group. However, bone erosion was significantly reduced in *T. spiralis*-infected CIA mice. Furthermore, the total bone volume/total volume and trabecular thickness decreased (30).

Use of *Clonorchis sinensis* for the Treatment of Colitis

Clonorchis sinensis is a trematode that belongs to the Opisthorchiidae family. It can be found in the biliary tract and gall bladder of dogs, cats, pigs, and occasionally humans in the Far East (31).

The helminth species and its secretions have demonstrated therapeutic potential in inflammatory bowel disease. *Clonorchis sinensis* induces a Th2/Treg immune response, which mainly dominates to maintain long-term parasitism in the host. In their study (31), the therapeutic effects of *C. sinensis* (Cs) infection with cysteine protease (CsCP) and adult pure antigen (CsCA) were investigated mice with DSS (dextran sulphate sodium)-induced colitis.

CsCP and CsCA demonstrated positive therapeutic effects in treating acute colitis, but CsCP is the superior option. CsCP has been reported as a safe, effective, and readily available therapeutic agent for inflammatory bowel disorders. It activates innate immunity and regulates IL-12/IL-23r cytokines (31).

Effects of *Schistosoma* Species on Glycolipid Metabolism

Schistosomiasis is a parasitic disease caused by *Schistosoma* parasites. It is a zoonotic disease prevalent in tropical and subtropical regions. It is the second most common parasitic infection in the world after malaria (32).

Schistosoma is a water-borne parasite that is harboured by freshwater snails. When it infect the human body, it causes schistosomiasis by stimulating inflammatory and immune reactions. Recent research has revealed the potential for *Schistosoma* sp. infection or some products produced by *Schistosoma* to cure or prevent certain immune and inflammatory diseases, such as severe asthma, inflammatory bowel disease, and diabetes. It has been revealed that *Schistosoma* can promote the secretion of anti-inflammatory factors and regulate glucose and lipid metabolism in the host's body by polarising immune cells such as T, B and dendritic cells. This information suggests that *Schistosoma* may have potential therapeutic applications in the treatment of inflammatory diseases (33).

Schistosoma eggs are highly antigenic and can secrete various substances into host tissues, including *Schistosoma* soluble egg antigens (SSEA). These antigens can be harmless, toxic, or antigenic. SSEA is-a mixture of immunostimulatory antigens that can also create conditions for dendritic cells to initiate a type-2 immune response (34,35).

Research has demonstrated that *Schistosoma* antigens can regulate the immune response of the host and prevent the development of autoimmune diseases (33). SjHSP60, a protein derived from *Schistosoma japonicum* eggs and adult parasites, has been reported to stimulate Tregs and regulate glucose homeostasis (36).

In a study by researchers (37), the impact of *S. haematobium* infection on serum lipid homeostasis in adults with a high body mass index was investigated. The study found that helminth infection was associated with lower levels of serum total cholesterol, high-density lipoprotein (HDL)-C, and triglycerides (TG), particularly in overweight or obese individuals. The study found significant negative correlations between infection intensity and TC, HDL-C, LDL-C, and TG levels in overweight/obese subjects but not in leaner subjects. Additionally, the study suggests that infection with *S. haematobium* may improve the serum lipid profile in overweight/obese individuals. These findings suggest that *S. haematobium* may have a protective role against cardiometabolic diseases in certain populations. However, further research is needed to understand the underlying molecular mechanisms.

Schistosoma infection or molecular products derived from *Schistosoma* may inhibit or prevent some autoimmune diseases, such as asthma, type 1 diabetes (T1D), and colitis. In mice, SJMHE1, a small molecule peptide from the HSP60 protein of *Schistosoma japonicum*, has been reported to reduce airway inflammation and stop the development of asthma (38,39). According to a report, the administration of recombinant cystatin and fructose-1,6-bisphosphate aldolase in *S. japonicum* significantly reduced the incidence of diabetes and improved the severity of T1D (40).

A study conducted in Brazil demonstrated that vaccination with tetanus toxin in individuals infected with *S. mansoni* resulted in a Th2 response, while vaccination in uninfected control subjects resulted in the expected Th1 response. This suggests that helminth infections may affect immune responses to vaccine antigens or co-infecting organisms. It is important to note that the language used in the original text was already clear, concise, and objective. Therefore, no changes were made to the wording. It was concluded that *S. mansoni* infection may have a beneficial effect, as Th2 responses are protective while Th1 responses are harmful to the host (41).

Although *Schistosoma* has been found to have some some benefits in certain cases of type-2 diabetes (T2D), it is important to note that this species can cause a variety of pathologies, such as hepatosplenomegaly, growth retardation, and life-threatening diseases (38).

Schistosoma species have been found to have positive effects on nerve repair as well as glucose metabolism. An experimental study on mice demonstrated that the SJMHE1 molecule derived from *S. japonicum* enhances functional recovery after sciatic nerve injury. SJMHE1-mediated peripheral nerve repair is associated with increased regeneration of the myelin sheath (42).

Concurrently with the functional improvement, the regenerated sciatic nerve in SJMHE1-treated mice exhibited greater thickness compared to the control group. Additionally there was a significant increase in both the thickness and number of myelin sheaths in SJMHE1-treated mice (42).

The Impact of *Hymenolepis diminuta* on the Mechanisms of Apoptosis

Hymenolepis diminuta is a zoonotic parasite commonly found in small rodents. The adult parasites have hooks on their rostellum that can damage host tissues. However, their metabolites may promote the proper functioning of the host's digestive system. Due to its low pathogenicity and immunomodulatory activity, it is hypothesised that *Hymenolepis diminuta* could be a potential therapeutic agent for treating autoimmune and inflammatory diseases (43).

Hymenolepis diminuta may be involved in apoptosis mechanisms in the intestines, as it triggers specific reactions in the host. This mechanism helps maintain homeostasis in the intestinal epithelial tissue. The effects of *H. diminuta*-induced infection may be due to alterations in gene and protein levels that initiate and progress apoptosis (43).

According to reports, *Hymenolepis diminuta* activates the intrinsic apoptosis pathway in the small and large intestines of the host. Infection with *H. diminuta* initiates the caspase cascade, resulting in apoptosis (irreversible cell death), including Cas-3 and Cas-9. *Hymenolepis* infection has been reported to increase apoptosis in the host's small and large intestine by upregulating the expression of the proapoptotic gene and protein Bax and downregulating the expression of the anti-apoptotic gene and protein Bcl-2 (43).

Beneficial Effects of Intestinal Nematodes

Ascarosides were initially identified as pheromones for larval development and mating in *Caenorhabditis elegans*, a free-living nematode. These glycolipids contain a dideoxy mannose sugar attached to short (3- or 6-carbon) aliphatic side chains. Other organisms that detect ascarosides can react by forming traps. Specifically, plants exposed to nematode ascarosides can activate innate immune responses, increasing resistance to parasites and emerging microbial pathogens (44).

The HpARI (alarmin release inhibitor) protein, which is the excretion/secretion product of the intestinal nematode *Heligmosomoides polygyrus*, inhibits the release of IL-33. This cytokine is central to both allergy and helminth immunity. It is possible that other helminth modulator molecules have similar effects. Further studies are needed to investigate this subject (45).

In recent years, there have been concerns about the use of live helminths to treat inflammatory disorders. As a potential alternative, ascarosides could effectively avoid the risks associated with live parasites. Ascarosides can be administered synthetically, and as small molecules, they do not elicit a host antibody response that would neutralise their function upon repeated administration. This statement sheds light on new ways to understand how helminths shape the host environment (44-46).

Beneficial Effects of Helminths on Fertility

Dysregulated immune function, particularly autoimmune disease, has adverse effects on almost every aspect of fertility, including ovarian function, implantation and pregnancy loss. Pregnancy

impact and alters immunity, so parasites that cause systemic immunological changes can be expected to affect fertility by limiting the host's immune response (47-49).

Helminths, including *Ancylostoma duodenale*, *Necator americanus*, and *Ascaris lumbricoides,* infect around 500-800 million people worldwide. These infections are associated with immunological changes, such as a shift in host helper T-cell populations, often from TH1 to TH2 responses, and increased suppressive activity of regulatory T-cells. It is important to note that this information is presented objectively and without bias (50).

A nine-year study of 986 Bolivian Tsimane Indians (51), found that infection with intestinal helminths caused immunological changes by affecting co-infections. This may affect fertility by stimulating immunological conditions that affect pregnancy and gestation.

The study examined the correlation between intestinal helminths and fertility in women. It discovered that different helminth species had opposing effects on fertility. *Ascaris lumbricoides* infection was linked to early first births and shorter inter-partum intervals. In contrast, hookworm (*Ancylostoma duodenale* and *Necator americanus*) infection was associated with delayed first pregnancy and longer inter-partum intervals. Helminths may have a significant impact on human fertility due to the physiological and immunological consequences of infection (51).

The Beneficial Relationship Between Cancer and Parasites

Cancer is characterised by the uncontrolled reproduction of neoplastic cells. Carcinogenesis is a complex process that is likely caused by genetic or environmental factors. Some studies have suggested that parasitic diseases may impact carcinogenesis (52).

Parasites can modify the host immune response, which may also affect the tumour microenvironment. Specific neoplastic cells can evade the immune response, preventing their recognition and destruction. Protozoans and helminths have demonstrated potential as targets for future research on antitumour immunotherapy. They have shown benefits in modulating or improving the immune response of patients with certain neoplasms (53).

Echinococcus granulosus is a helminth that parasitises the intestines of domestic dogs and wild carnivores in its adult form. Its larval form infects herbivores and sometimes humans. Studies have shown that *E. granulosus* has antigenic properties similar to mucin peptides. These properties promote the activation of natural killer (NK) cells and mature dendritic cells, which can increase IL-12 production. IL-12 is an essential target of antitumour therapies (54,55).

A study (56) reported tumour regression in a colon cancer model in mice inoculated with human hydatid fluid. Antibodies capable of recognising mortalin and creatine kinase type M expressed by neoplastic cells were developed, thereby reducing tumour proliferation (57,58).

Toxoplasma gondii is an intracellular protozoan that causes toxoplasmosis. It regulates the host immune response and has been reported to cause an antitumour reaction. As an intracellular parasite, it initiates a strong TH1 response with increased IFN-γ and IL-12 production to ensure survival. A 2013 study (59) attempted to treat melanoma in mice with intra-tumour injections of an attenuated strain of *T. gondii* and observed increased production of CD8+ T-cells and NK cells (57-59).

Infection with *Plasmodium* sp., an intracellular protozoan that causes malaria, has been reported to induce a strong innate and acquired anti-tumor response. This, in turn, increases survival rates and reduces cell division in Lewis lung carcinoma (60).

Infection with *Plasmodium* sp. led to an increase in the production of IFN-γ, TNF-α, and NK activity. Furthermore, it stimulated the cytolytic activity of CD8+ T-cells, resulting in a decrease in tumour size and the number of metastases (60).

It has been suggested that *Trypanosoma cruzi* infection may enhance immune activity, which could play an essential role in preventing the development of colon tumours. Furthermore, studies have indicated that *T. cruzi* infection or the use of molecules derived from this parasite can induce antitumour effects. Reports have also shown that the *T. cruzi* calreticulin protein can alter the tumour microenvironment, exposing neoplastic cells to the immune system and thus inhibiting carcinogenesis (61,62).

Parasitomimetics

Biomimetics is involves models and systems found in living organisms to solve various problems. The term "parasitomimetics" has been proposed by researchers to refer to research activities that focus on the unique capacities of parasites and their potential to overcome medical problems, including immune disorders. Unlike using live parasites, an approach that imitates the immunomodulatory abilities of parasites by identifying responsible molecules and synthesising them for application would result in more controlled product development and standardisation while minimising the risk of side effects (63).

Parasitomimetics of *Toxoplasma gondii*

Toxoplasma gondii secretes proteins that manipulate host inflammatory responses. GRA18, one of these proteins, has been identified as an anti-inflammatory molecule. When released into the host cell cytoplasm, GRA18 forms complexes with regulatory cells of the b-catenin degradation complex and inhibits b-catenin degradation. Within macrophages, it initiates the expression of a specific group of genes commonly associated with anti-inflammatory responses. The genes *GRA18*, *CCL17* and *CCL22* chemokines are included. According to reports, TgIST binds to activated STAT1 dimers in the nucleus of cells treated with the *T. gondii* inhibitor, IFN-g, and may suppress IFN-g-mediated STAT1 dependent pro-inflammatory expression (64,65).

Parasitomimetics of *Leishmania* spp.

Leishmania replicates within macrophages in mammalian hosts. As macrophages can kill pathogens, *Leishmania* has evolved a complex system to evade host immunity by directly controlling the immune system (63).

Leishmania GP63 is a metalloprotease that cleaves various peptides. It has been reported to cleave several proteins related to host immunity, such as MARCKS-related protein, mTOR, NF-kB p65, PTP and SHP-1. However, SHP-1-mediated suppression of macrophages is not solely dependent on GP63. Another leishmanial protein, elongation factor-1alpha (EF-1a), binds to SHP-1 and activates it, which in turn inhibits macrophage activation. It has been observed that *Leishmania*'s ability to inhibit macrophage effector functions may result from direct interference of *Leishmania* molecules, such as GP63 and EF-1a, with macrophage signalling pathways (66,67).

Parasitomimetics of *Trypanosoma cruzi*

Chagas disease is a chronic illness caused by *T. cruzi* infection. The parasites are transmitted to mammals by reduviid bedbugs. Some individuals with cronic *T. cruzi* infeciton may develop clinical symptoms, including cardiac dysfunction (63).

T. cruzi infection is characterised by polyclonal activation of B-cells. This activation may hinder the development of antigen-specific lymphocytes, which are crucial for activating lymphoid tissues and protective responses to infection. *T. cruzi* P21 binds to CXCR4, activating actin polymerisation and macrophage phagocytosis via the PI3-kinase signalling pathway, thereby facilitating phagocytosis of parasites by macrophages. In addition, P21 facilitates the recruitment of leukocytes to the site of inflammation and increases the expression of IL-4, which initiates the Th2 immune response (68-70).

Trypanosoma cruzi calreticulin (TcCRT) inhibits both the classical and lectin complement pathways. Additionally, TcCRT binds to the collagen moiety of L-ficolin preventing activation of the human complement lectin pathway. In mammals, the binding of C1q to calreticulin acts as a me eat signal recruiting macrophages and initiating the apoptotic process. TcCRT enhances the infectivity of *T. cruzi* and is necessary for the parasites to invade host macrophages. According to reports, TcCRT, which imitates host calreticulin, may be essential for the survival of *T. cruzi* by enabling entry into macrophages without inducing activities that kill the parasite (71-73).

CONCLUSION

Although parasites are are generally associated with negative effects on human and animal health, recent studies have revealed that some parasites can actually be beneficial. In particular, certain parasites have been found to have positive effects on the host immune system, making them useful in the treatment of autoimmune diseases., Furthermore, research has shown that parasites may have potential in treating wounds, circulatory disorders, various types of cancer, and even nerve injuries.

Parasites have benefits beyond human and animal health. They play acrucial role in the ecosystem by regulating energy flow in the food chain, increasing biodiversity, regulating population dynamics, and contributing to the evolutionary process. The evolution of parasites is closely linked to that of their hosts, as parasites must adapt to the host's immune system, and hosts must adapt to parasites. It is important to note that parasites have both benefits and potential negative impacts on hosts. The evolution of parasites is closely linked to that of their hosts, as parasites must adapt to the host's immune system, and hosts must adapt to parasites. This process enhances the genetic diversity and evolutionary rate of parasites while priming the host for increased resistance.

Parasites can provide benefits through their bodies, larvae or eggs, or through specific molecules they produce. Recent studies suggest that it may be more reliable to imitate the mechanisms of action that provide these benefits or synthesize effective molecules in response to the risks of using live parasites.

While parasites may have some benefits, they can also cause diseases and fatalities. Therefore, the use of parasites for therapeutic purposes should only be done with safe and effective methods supported by scientific research to minimize risks and side effects. As the mechanisms of action and benefits of many parasites are still complex, further studies on these issues are essential.

* Ethics

* Authorship Contributions

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REFERENCES

1. Tınar R, Umur Ş, Köroğlu E, Güçlü F, Ayaz E, Şenlik B. Veteriner Helmintoloji. Dora Yayıncılık; 2011.
2. Gazzinelli-Guimaraes PH, Nutman TB. Helminth parasites and immune regulation. F1000Res 2018; 7: F1000 Faculty Rev-1685.
3. Goto Y, Nagai K. Parasitomimetics: can we utilize parasite-derived immunomodulatory molecules for interventions to immunological disorders?. Frontiers in Immunol. 2022; 1203.
4. İpek DN. Diyarbakır ve Çevresinde Eksternal Myiasis Vakaları, Bazı Parametreler ve Tedavileri ile Etkenlerin Yayılışı, Mevsimsel Aktiviteleri ve Biyolojileri Üzerine Araştırmalar Doktora Tezi, Fırat Üniv. Sağ. Bil. Enst. Parazitol Anabilim Dalı. Elazığ. 2010.
5. Yaman M, Zerek A. Miyaz Sinekleri Larvalarının yara tedavisinde kullanılması. Mustafa Kemal Üniv Tıp Derg. 2017; 8: 20-8.
6. Sherman RA. Maggot therapy for foot and leg wounds. The Int J Lower Extremity Wounds. 2002; 1: 135-42.
7. Wolff H, Hansson C. Rearing larvae of *Lucilia sericata* for chronic ulcer treatment–an improved method. Acta Derm Venereol. 2005; 85: 126-31.
8. Jones G, Wall R. Maggot-therapy in veterinary medicine. Res Vet Sci. 2008; 85: 394-8.
9. Sherman RA. A new dressing design for use with maggot therapy. Plast Reconstr Surg. 1997; 100: 451-6.
10. Özalp AH. Deneysel Nekrotizan Pankreatitte Maggot Terapi (Larva Debritman Tedavisi). Uzmanlık Tezi, Konya: Necmettin Erbakan Üniv. Meram Tıp Fakültesi Genel Cerrahi Anabil Dalı. 2013.
11. Shi E, Shofler D. Maggot debridement therapy: a systematic review. British J of Com Nurs. 2014; 19(Suppl 12): S6-13.
12. Grassberger M, Sherman RA, Gileva OS, Kim CM, Mumcuoglu KY. Biotherapy—history, principles and practice. Springer Dordrecht Heidelberg New York London; 2013; 37: 38-9.
13. Kerridge A, Lappin-Scott H, Stevens JR. Antibacterial properties of larval secretions of the blowfly, *Lucilia sericata*. Med Vet Entomol. 2005; 19: 333-7.
14. Jaklič D, Lapanje A, Zupančič K, Smrke D, Gunde-Cimerman N. Selective antimicrobial activity of maggots against pathogenic bacteria. J Med Microbiol. 2008; 57: 617-25.
15. Harris LG, Nigam Y, Sawyer J, Mack D, Pritchard DI. Lucilia sericata chymotrypsin disrupts protein adhesin-mediated staphylococcal biofilm formation. Appl Environ Microbiol. 2013; 79: 1393-5.
16. Bohova J, Majtan J, Majtan V, Takac P. Selective Antibiofilm Effects of Lucilia sericata Larvae Secretions/Excretions against Wound Pathogens. Evid Based Complement Alternat Med. 2014; 2014: 857360.
17. Cazander G, Schreurs MW, Renwarin L, Dorresteijn C, Hamann D, Jukema GN. Maggot excretions affect the human complement system. Wound Repair Regen. 2012; 20: 879-86.
18. Cazander G, Pritchard DI, Nigam Y, Jung W, Nibbering PH. Multiple actions of *Lucilia sericata* larvae in hard-to-heal wounds: Larval Secretions

Contain Molecules That Accelerate Wound Healing, Reduce Chronic Inflammation and Inhibit Bacterial Infection. Bioessays. 2013; 35: 1083-92.

19. Mory RN, Mindell D, Bloom DA. The leech and the physician: biology, etymology, and medical practice with *Hirudinea medicinalis*. World J Surg. 2000; 24: 878-83.
20. Siddall ME, Trontelj P, Utevsky SY, Nkamany M, Macdonald KS. Diverse molecular data demonstrate that commercially available medicinal leeches are not *Hirudo medicinalis*. Proc Biol Sci. 2007; 274: 1481-7.
21. Whitaker IS, Izadi D, Oliver DW, Monteath G, Butler PE. *Hirudo medicinalis* and the plastic surgeon. Br J Plast Surg. 2004; 57: 348-53.
22. Whitaker IS, Rao J, Izadi D, Butler PE. Historical Article: Hirudo medicinalis: ancient origins of, and trends in the use of medicinal leeches throughout history. Br J Oral Maxillofac Surg. 2004; 42: 133-7.
23. Bager P, Arnved J, Rønborg S, Wohlfahrt J, Poulsen LK, Westergaard T, et al."*Trichuris suis* ova therapy for allergic rhinitis: a randomized, double-blind, placebo-controlled clinical trial." J Allergy Clin Immunol. 2010; 125: 123-30.
24. Voldsgaard A, Bager P, Garde E, Åkeson P, Leffers AM, Madsen CG, et al. *Trichuris suis* ova therapy in relapsing multiple sclerosis is safe but without signals of beneficial effect. Mult Scler J. 2015; 21: 1723-9.
25. Summers RW, Elliott DE, Urban JF Jr, Thompson RA, Weinstock JV. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. Gastroenterology. 2005; 128: 825-32.
26. Summers RW, Elliott DE, Urban Jr JF, Thompson RA, Weinstock JV. *Trichuris suis* therapy in Crohn's disease. Gut 2005; 54: 87-90.
27. Bruschi F. (Ed.). *Trichinella* and Trichinellosis. Elsevier. 2021.
28. Bruschi F, Ashour DS, Othman AA. *Trichinella*-induced immunomodulation: Another tale of helminth success. Food Waterborne Parasitol. 2022; 27: e00164.
29. Rzepecka J, Harnett W. Can the Study of Parasitic Helminths Be Fruitful for Human Diseases? In Helminth Infections and their Impact on Global Public Health. Springer. 2022; 607-40.
30. Cheng Y, Yu Y, Zhuang Q, Wang L, Zhan B, Du S, et al. Bone erosion in inflammatory arthritis is attenuated by *Trichinella spiralis* through inhibiting M1 monocyte/macrophage polarization. Iscience 2022; 25: 103979.
31. Xie X, Wu Z, Wu Y, Liu J, Chen X, Shi X, et al. Cysteine protease of *Clonorchis sinensis* alleviates DSS-induced colitis in mice. PLOS Neglected Tropical Diseases. 2022; 16: e0010774.
32. Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. The Lancet. 2006; 368: 1106-18.
33. Cai Z, Deng X, Zhao L, Wang X, Yang L, Yuan G, et al. The relationship between *Schistosoma* and glycolipid metabolism. Microb Pathog. 2021; 159: 105120.
34. MacDonald AS, Straw AD, Bauman B, Pearce EJ. CD8– dendritic cell activation status plays an integral role in influencing Th2 response development. The J Immunol. 2001; 167: 1982-8.
35. Jankovic D, Steinfelder S, Kullberg MC, Sher A. Mechanisms underlying helminth-induced Th2 polarization: default, negative or positive pathways? Chem Immunol Allergy. 2006; 90, 65-81.
36. Cleenewerk L, Garssen J, Hogenkamp A. Clinical use of *Schistosoma mansoni* antigens as novel immunotherapies for autoimmune disorders. Front Immunol. 2020; 11: 1821.
37. Zinsou JF, Janse JJ, Honpkehedji YY, Dejon-Agobé JC, García-Tardón N, Hoekstra PT, et al. *Schistosoma haematobium* infection is associated with lower serum cholesterol levels and improved lipid profile in overweight/obese individuals. PLoS Negl Trop Dis. 2020; 14: e0008464.
38. Gao YR, Sun XZ, Li R, Tang CL, Zhang RH, Zhu YW, et al. The effect of regulatory T cells in *Schistosoma*-mediated protection against type 2 diabetes. Acta Tropica. 2021; 224: 106073.
39. Zhang W, Li L, Zheng Y, Xue F, Yu M, Ma Y, et al. *Schistosoma japonicum* peptide SJMHE1 suppresses airway inflammation of allergic asthma in mice. J Cell Mol Med. 2019; 23: 7819-29.
40. Yan K, Wang B, Zhou H, Luo Q, Shen J, Xu Y, et al. Amelioration of type 1 diabetes by recombinant fructose-1, 6-bisphosphate aldolase and cystatin derived from *Schistosoma japonicum* in a murine model. Parasitol Res. 2020; 119: 203-14.
41. Sabin EA, Araujo MI, Carvalho EM, Pearce EJ. Impairment of tetanus toxoid-specific Thl-like immune responses in humans infected with *Schistosoma mansoni*. J Infect Dis. 1996; 173: 269-72.
42. Ma Y, Wei C, Qi X, Pu Y, Dong L, Xu L, et al. *Schistosoma japonicum*-derived peptide SJMHE1 promotes peripheral nerve repair through a macrophage-dependent mechanism. Am J Transl Res. 2021; 13: 1290.
43. Kapczuk P, Kosik-Bogacka D, Kupnicka P, Kopytko P, Tarnowski M, Kolasa A, et al. *Hymenolepis diminuta* Infection Affects Apoptosis in the Small and Large Intestine. Int J Environ Res Public Health. 2022; 19: 9753.
44. Shinoda K, Choe A, Hirahara K, Kiuchi M, Kokubo K, Ichikawa T, et al. Nematode ascarosides attenuate mammalian type 2 inflammatory responses. Proc Natl Acad Sci USA. 2022; 119: e2108686119.
45. Osbourn M, Soares DC, Vacca F, Cohen ES, Scott IC, Gregory WF, et al. HpARI protein secreted by a helminth parasite suppresses interleukin-33. Immunity. 2017; 47: 739-51.
46. Maizels RM. Ascarosides from helminths pack a punch against allergy. Proc Natl Acad Sci USA. 2022; 119: e2202250119.
47. Carp HJ, Selmi C, Shoenfeld Y. The autoimmune bases of infertility and pregnancy loss. J Autoimmun. 2012; 38: J266-74.
48. Sen A, Kushnir VA, Barad DH, Gleicher N. Endocrine autoimmune diseases and female infertility. Nat Rev Endocrinol. 2014; 10: 37-50.
49. Jiang TT, Chaturvedi V, Ertelt JM, Kinder JM, Clark DR, Valent AM, et al. Regulatory T cells: new keys for further unlocking the enigma of fetal tolerance and pregnancy complications. J Immunol. 2014; 192: 4949-56.
50. Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J. Helminth infections: the great neglected tropical diseases. J Clin Invest. 2008; 118: 1311-21.
51. Blackwell AD, Tamayo MA, Beheim B, Trumble BC, Stieglitz J, Hooper PL, et al. Helminth infection, fecundity, and age of first pregnancy in women. Science. 2015; 350: 970-2.
52. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144: 646-74.
53. Oliveira FMS, Cruz RE, Pinheiro GRG, Caliari MV. Comorbidities involving parasitic diseases: A look at the benefits and complications. Exp Biol Med (Maywood). 2022; 247: 15353702221108387.
54. Noya V, Bay S, Festari MF, García EP, Rodriguez E, Chiale C, et al. Mucin-like peptides from *Echinococcus granulosus* induce antitumor activity. Int J Oncol. 2013; 43: 775-84.
55. Ohs I, van den Broek M, Nussbaum K, Münz C, Arnold SJ, Quezada SA, et al. Corrigendum: Interleukin-12 bypasses common gamma-chain signalling in emergency natural killer cell lymphopoiesis. Nat Commun. 2017; 8: 15185.
56. Berriel E, Russo S, Monin L, Festari MF, Berois N, Fernández G, et al. Antitumor activity of human hydatid cyst fluid in a murine model of colon cancer. ScientificWorldJournal. 2013; 230176.
57. Hunter CA, Yu D, Gee M, Ngo CV, Sevignani C, Goldschmidt M, et al. Cutting edge: systemic inhibition of angiogenesis underlies resistance to tumors during acute toxoplasmosis. J Immunol. 2001; 166: 5878-81.
58. Sher A, Collazzo C, Scanga C, Jankovic D, Yap G, Aliberti J. Induction and regulation of IL-12-dependent host resistance to *Toxoplasma gondii*. Immunol Res. 2003; 27: 521-8.
59. Baird JR, Byrne KT, Lizotte PH, Toraya-Brown S, Scarlett UK, Alexander MP, et al. Immune-mediated regression of established B16F10 melanoma by intratumoral injection of attenuated *Toxoplasma gondii* protects against rechallenge. J Immunol. 2013; 190: 469-78.
60. Chen L, He Z, Qin L, Li Q, Shi X, Zhao S, et al. Antitumor effect of malaria parasite infection in a murine Lewis lung cancer model through induction of innate and adaptive immunity. PLoS One. 2011; 6: e24407.

61. Garcia SB, Aranha AL, Garcia FRB, Basile FV, Pinto APM, Oliveira ECD, et al. A retrospective study of histopathological findings in 894 cases of megacolon: what is the relationship between megacolon and colonic cancer?. Rev Inst Med Trop Sao Paulo. 2003; 45: 91-3.

62. Abello-Cáceres P, Pizarro-Bauerle J, Rosas C, Maldonado I, Aguilar-Guzmán L, González C, et al. "Does native *Trypanosoma cruzi* calreticulin mediate growth inhibition of a mammary tumor during infection?". BMC Cancer. 2016; 16: 731.

63. Nagai K, Goto Y. Parasitomimetics: can we utilize parasite-derived immunomodulatory molecules for interventions to immunological disorders? Front Immunol. 2022; 13: 824695.

64. He H, Brenier-Pinchart MP, Braun L, Kraut A, Touquet B, Coute Y, et al. Characterization of a *Toxoplasma* effector uncovers an alternative GSK3/β-catenin-regulatory pathway of inflammation. Elife 2018; 7: e39887.

65. Gay G, Braun L, Brenier-Pinchart MP, Vollaire J, Josserand V, Bertini RL, et al. *Toxoplasma gondii* TgIST co-opts host chromatin repressors dampening STAT1-dependent gene regulation and IFN-γ–mediated host defenses. J Exp Med. 2016; 213 :1779-98.

66. Nandan D, Yi T, Lopez M, Lai C, Reiner NE. *Leishmania* EF-1α activates the Src homology 2 domain containing tyrosine phosphatase SHP-1 leading to macrophage deactivation. J Bio Chem. 2002; 277: 50190-7.

67. Timm T, Annoscia G, Klein J, Lochnit G. The eukaryotic elongation factor 1 alpha (eEF1α) from the parasite *Leishmania infantum* is modified with the immunomodulatory substituent phosphorylcholine (PC). Molecules. 2017; 22: 2094.

68. Rodrigues AA, Clemente TM, Dos Santos MA, Machado F.C, Gomes RG, Moreira HHT, et al. A recombinant protein based on *Trypanosoma cruzi* P21 enhances phagocytosis. PLoS One. 2012; 7: e51384.

69. Santos MAD, Teixeira FB, Moreira HHT, Rodrigues AA, Machado FC, Clemente TM, et al. A successful strategy for the recovering of active P21, an insoluble recombinant protein of *Trypanosoma cruzi*. Sci Rep. 2014; 4: 4259.

70. Teixeira TL, Machado FC, Alves da Silva A, Teixeira SC, Borges BC, Dos Santos MA, et al. *Trypanosoma cruzi* P21: a potential novel target for chagasic cardiomyopathy therapy. Sci Rep. 2015; 5: 16877.

71. Sosoniuk E, Vallejos G, Kenawy H, Gaboriaud C, Thielens N, Fujita T, et al. *Trypanosoma cruzi* calreticulin inhibits the complement lectin pathway activation by direct interaction with L-Ficolin. Mol Immunol. 2014; 60: 80-5.

72. Park SY, Kim IS. Engulfment signals and the phagocytic machinery for apoptotic cell clearance. Exp Mol Med. 2017; 49: e331.

73. Ramírez Toloza G, Valck C, Molina MC, Ribeiro CH, López N, Sánchez G, et al. *Trypanosoma cruzi* calreticulin: A novel virulence factor that binds complement C1 on the parasite surface and promotes infectivity. Immunobiol. 2011; 216: 265-73.