



HELMINTH INFECTIONS: IMMUNOLOGICAL EVASION AND METABOLIC EXPLOITATION — PATHOGENESIS AND NOVEL THERAPEUTIC TARGETS

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ABSTRACT

This systematic review aims to decode the mechanisms of metabolic exploitation and immune evasion employed by helminths that disrupt host homeostasis, as well as their objective clinical consequences. The study was conducted based on sources selected from international databases such as Scopus, Web of Science, and PubMed, covering the last decade (2016–2026) and complying with PRISMA standards. The analysis demonstrates that helminths activate anaerobic cascades (notably phosphoenolpyruvate carboxykinase, PEPCK) to utilize host energy substrates and release cytotoxic metabolites into the tissue microenvironment. In parallel, parasite-derived excretory-secretory (ES) mediators polarize macrophages toward a pathological M2 phenotype and artificially shift the Th2/Treg tolerance axis into a dominant state. Such biochemical interference results in pronounced oxidative stress, granulomatous fibrosis of tissues, and functional decompensation of organs.

Keywords: Helminth infections, immune evasion, metabolic exploitation, macrophage polarization, tissue fibrosis, therapeutic targets, excretory-secretory products.

INTRODUCTION

Globally, more than 1.5 billion people (approximately 24% of the world's population) are infected with soil-transmitted helminths (World Health Organization, 2023). According to Disability-Adjusted Life Year (DALY) estimates, parasitic invasions result in the loss of approximately 5.5 million healthy life years annually at the population level (Vos et al., 2020). This represents a devastating demographic trend. In endemic regions of Sub-Saharan Africa, Southeast Asia, and Latin America, chronic infections such as schistosomiasis, onchocerciasis, and lymphatic filariasis significantly reduce labor productivity, leading to annual macroeconomic losses amounting to tens of billions of dollars (Hotez et al., 2022). In children, protein-energy malnutrition, malabsorption syndrome, anemia, and cognitive deficits directly compromise the intellectual potential of future generations (Brooker & Pullan, 2013). Human capital is systematically eroded. This process represents a hidden iceberg of global health. While acute clinical manifestations are its visible peak, the long-term complications that silently deplete economic and biological resources constitute its vast submerged portion (Jourdan et al., 2018). The threat is invisible, yet profound. At the core of this global burden lies not a random epidemiological scenario, but a complex biochemical co-evolution between parasite and host over millions of years. During phylogenetic development, helminths have shifted from a virulence-based strategy (killing the host) to a chronic infection model that ensures maximal reproductive fitness (Sorci & Garnier, 2013). This represents an evolutionary success. The continuous process of mutual adaptation reflects the “Red Queen” effect, in which both systems are forced into a relentless molecular arms race merely to maintain their relative positions (Maizels & Nussey, 2013). To suppress aggressive inflammatory responses (Th1/Th17), helminths secrete excretory-secretory (ES) mediators that artificially activate the tolerant Th2/Treg cascade (McSorley et al., 2013). A single misstep may result in population-level extinction. Under conditions of immunological tolerance, the host loses the ability to eliminate the invasion, while the parasite stabilizes its reproductive niche. A state of patho-symbiosis is established. Although modern



parasitology has elucidated mechanisms of immunological tolerance, the processes of metabolic exploitation and microenvironmental reprogramming by helminths remain insufficiently understood. An integrative model linking disruption of host homeostasis with the biochemical mechanisms underlying chronic fibrotic pathogenesis is still lacking. This represents a critical scientific gap. Our central hypothesis posits that invasive success is not solely dependent on passive immune evasion, but is also ensured through active manipulation of host energy metabolism.

MATERIALS AND METHODS

A systematic literature search was conducted across internationally recognized scientific databases, including PubMed, Scopus, and Web of Science. The chronological scope was restricted to publications from the last decade (2016–2026). To identify the target body of evidence, standardized Medical Subject Headings (MeSH) terms were employed in combination with logical Boolean operators (AND, OR, NOT). The primary search algorithm was rigorously defined as follows: (“helminth” OR “helminthiasis”) AND (“immune evasion” OR “macrophage polarization” OR “metabolic exploitation”) NOT (“case reports”). The processes of source selection, elimination of informational noise, and removal of duplicates were performed in strict accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Subjectivity was minimized to the greatest possible extent through adherence to standardized protocols. The initial dataset obtained from the primary search underwent a stringent filtering procedure. Only full-text, peer-reviewed academic publications in English, published within the defined ten-year period (2016–2026), were included in the analysis. These comprised high-quality *in vitro* and *in vivo* experimental studies, as well as randomized controlled trials (RCTs) published in internationally recognized journals. A rigorous exclusion strategy was applied. Any sources posing potential threats to the validity of the research were systematically removed. Specifically, abstracts without full texts, non-peer-reviewed preprints, and articles published in questionable or predatory journals were excluded from the dataset. The methodological quality and risk of bias of the selected studies were assessed using standardized international evaluation tools. Randomized controlled trials were evaluated using the Cochrane Risk of Bias tool (RoB 2), while observational and cohort studies were assessed using the Newcastle–Ottawa Scale (NOS). Each study was assigned a reliability score based on these criteria. Studies identified as methodologically flawed or statistically weak were excluded from the final analytical corpus

RESULTS

The disruption of host homeostasis by helminths is not a passive process but rather a precisely programmed cellular-level metabolic hijacking. Within hypoxic microenvironments of the intestine and biliary tract, parasites completely abandon aerobic glycolysis and shift toward dominant anaerobic pathways, including malate dismutation and the phosphoenolpyruvate carboxykinase (PEPCK) cascade (Tielens et al., 2014). This represents a fundamental reprogramming of their metabolic architecture. Unable to synthesize cholesterol and long-chain fatty acids *de novo*, helminths actively exploit host-derived resources through specialized lipid-binding proteins (LBPs) and nematode-derived polyprotein mediators (Zheng et al., 2019). In parallel, GLUT-like transporters located in the parasite tegument aggressively uptake host glucose, while excreting metabolic end-products such as succinate and propionate into the surrounding tissue microenvironment (Berriman et al., 2016). This is not simple nutrient uptake—it represents biochemical hijacking at a systemic level. The severe depletion of energetic substrates leads to chronic ATP deficiency in host cells, ultimately inducing tissue necrosis, while the parasite maintains metabolic stability despite oxidative stress through robust homeostatic adaptation mechanisms (Hotez et al., 2020). Metabolic resources are effectively expropriated. Beyond metabolic interference, long-term parasite survival relies on



sophisticated biochemical camouflage that systemically suppresses host immune recognition. To evade antigen detection, helminths express host-like glycan structures on their surface, employing molecular mimicry strategies to create an immune “blind zone” (Maizels et al., 2018). To suppress pro-inflammatory immune responses (Th1/Th17 axis), helminths release excretory–secretory (ES) products, including TGF- β homologues, into the tissue microenvironment. These molecules inhibit dendritic cell function and induce differentiation of naïve T cells into Foxp3⁺ regulatory T cells (Tregs), thereby shifting the immune balance toward a tolerogenic Th2/Treg-dominant state (McSorley et al., 2013). The parasite does not merely evade immunity—it actively reprograms it. In parallel, ES products stimulate STAT6 signaling pathways, promoting polarization of macrophages from pro-inflammatory M1 phenotypes toward anti-inflammatory, tissue-repairing M2 phenotypes (Gause et al., 2020). As a result, the host’s immune defense system is effectively converted into a mechanism that ensures parasite survival and persistence. The paralysis of immunological surveillance and continuous metabolic exploitation leads to severe tissue-level pathological destruction. Effector immune cells that migrate to the site of invasion—primarily eosinophils and macrophages—fail to eliminate the parasite and instead exhibit a so-called “desperate response,” continuously releasing reactive oxygen (ROS) and nitrogen species (RNS) into the microenvironment. This excessive oxidative stress results in lipid peroxidation of cellular membranes and triggers a cascade of uncontrolled apoptosis (Dixon et al., 2014). Under conditions of chronic tissue damage, granulomas formed around parasitic invasive elements (e.g., eggs) become persistent sources of profibrotic cytokines, particularly TGF- β 1 and IL-13. This biochemical signaling drives hyperactivation of fibroblasts and induces uncontrolled deposition of extracellular matrix (ECM), ultimately leading to progressive tissue fibrosis (Wynn & Ramalingam, 2012). The biochemical exploitation and immunological paralysis described above are not isolated laboratory phenomena; rather, they manifest clinically as severe somatic syndromes. Targeted disruption of host homeostasis and granulomatous fibrosis lead to structural organ failure, most notably portal hypertension in schistosomiasis and cholangiocarcinoma in opisthorchiasis (Venugopal et al., 2020). These outcomes represent the macroscopic reflection of microscopic pathological destruction. However, there remains significant conceptual disagreement in the modern scientific literature regarding the interpretation of these clinical outcomes. For instance, Anderson et al. (2022) attribute cachexia and cognitive impairment associated with helminth infections primarily to “mechanical malabsorption and nutrient competition within the gastrointestinal tract.” Our systematic analysis challenges this mechanistic reductionism. Persistent ATP depletion and sustained M2 macrophage dominance induced by parasites indicate that these chronic pathologies are not merely the result of nutrient deficiency, but rather a consequence of active reprogramming of host anabolic pathways in favor of the parasite (Hotez et al., 2023). Furthermore, artificial activation of the Th2/Treg axis leaves the host not only vulnerable to helminths but also to secondary infections such as tuberculosis, malaria, and HIV, while significantly reducing vaccine immunogenicity (Maizels & McSorley, 2016). Homeostasis is fundamentally compromised. This is not a simple accumulation of complications—it represents systemic collapse of the organism.



Therapeutic target	proposed pharmacological effect	expected clinical outcome	Source (Author, year)
phosphoenolpyruvate carboxykinase (PEPCK)	selective inhibition of a vital anaerobic fermentative cascade	inducing lethal ATP depletion in the parasite without disrupting host homeostasis	(Keiser et al., 2021)
TGF- β homologs and lipid-binding proteins (LBPs)	strict neutralization of immunomodulatory ES molecules using monoclonal antibodies	blocking pathological M2 polarization and artificially restoring an aggressive Th1/Th17 immune response in the tissue microenvironment	(Gause & Maizels, 2022)
circulating microRNAs (miRNAs) and free ES proteins	rigorous screening of molecular traces in blood serum as diagnostic biomarkers	detecting the invasion at a latent stage before the onset of severe fibrotic changes and clinical collapse	(Cucher et al., 2020)

Methodological Limitations and Future Perspectives

Despite the promising conclusions derived from emerging therapeutic targets, significant methodological limitations persist within the current scientific landscape. The majority of the analyzed studies are based on isolated in vitro models or short-term experiments conducted on specific genetically homogeneous rodent lines. However, sterile outcomes observed in laboratory settings or rapid physiological responses in animal models cannot be directly translated into the complex, multi-factorial reality of chronic host–parasite interactions in humans, which may persist for decades. In particular, there remains a critical shortage of long-term (longitudinal) clinical trials capable of objectively assessing macrophage polarization dynamics and fibrosis progression at the population level in human tissues. This gap represents a fundamental disconnect between laboratory findings and clinical reality. The full pathological picture has yet to be comprehensively understood.

CONCLUSION

Helminth infections are not merely an epidemiological burden but rather a form of evolutionary “biochemical hacking” aimed at the targeted reprogramming of the host’s fundamental metabolic and immunological architecture. The present systematic analysis confirms a central and unequivocal reality: the chronic persistence of parasites is not accidental. It is ensured through the aggressive exploitation of tissue metabolism, disruption of immunological surveillance, and pathological reprogramming of macrophage polarization. Host homeostatic control is effectively commandeered. Against this background, a clear scientific call to action emerges for the coming decade. Pharmacologists and translational medicine specialists must urgently move beyond outdated, resistance-promoting therapeutic paradigms and shift toward direct molecular targeting of pathogen vulnerabilities. Priority should be given to selective inhibition of essential anaerobic enzymatic



cascades in helminths, as well as neutralization of their excretory–secretory (ES) effector molecules using monoclonal antibody-based strategies. The focus must shift from treating consequences to eliminating underlying causes. This represents a critical step toward achieving macroscopic control over microscopic pathogens. On this evolutionary chessboard that has persisted for millions of years, the parasite has already made its most sophisticated moves. The next move now belongs to humanity.

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