DOI: https://doi.org/10.54393/fbt.v5i4.210

FUTURISTIC BIOTECHNOLOGY
https://fbtjournal.com/index.php/fbt
ISSN (E): 2959-0981, (P): 2959-0973
Vol 05 Issue 04, (Oct-Dec, 2025)

Review Article

OPEN ACCESS

Cytokine Regulation of Immune Responses in Parasitic Diseases: A Review

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ARTICLE INFO

Keywords:
Cytokine Regulation, Immune Response, Parasitic Diseases, Immunomodulation, Host-Parasite Interaction

How to Cite:
Saqlain, M., Waris, A., Rizwan, A., Wasif, Z., Fatima, S., Hayat, S., Abbas, S., & Khan, A. A. (2025). Cytokine Regulation of Immune Responses in Parasitic Diseases: A Review: Cytokine Regulation of Immune Responses in Parasitic Diseases. Futuristic Biotechnology, 5(4), 27-34. https://doi.org/10.54393/fbt.v5i4.210

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Received Date: 16th September, 2025
Revised Date: 3rd November, 2025
Acceptance Date: 11th November, 2025
Published Date: 30th November, 2025

ABSTRACT

The immune regulation in parasitic infections plays a central role in cytokine mediation of host defense and disease pathology. It is an integrative review that summarizes the current molecular and quantitative data on the dynamics of cytokines in major parasitic infections, malaria, leishmaniasis, trypanosomiasis, and schistosomiasis. A methodical search of the literature was carried out in PubMed, Scopus, and Web of Science (2010-2025) and included specific inclusion and exclusion criteria. Descriptive analysis of quantitative cytokine concentration ranges and cytokine ratios was conducted based on heterogeneity of study designs. The figures were made with Figma software to be visually accurate and clear. The results have shown that the outcome of infections depends mostly on the balance between pro-inflammatory (e.g., TNF-α, IFN-γ) and regulatory cytokines (IL-10, TGF-β). Severity of the disease is associated with disrupted cytokine ratios, instead of cytokine abundance. Molecular mimicry and JAK-STAT and NF-κB modulations are some of the ways used by parasites to sustain chronicity by exploiting these cytokine pathways. A combination of comparative cytokine profiles shows common immunoregulatory principles between parasitic infections and cytokine ratios as a potential biomarker of disease progression or immune response to therapeutic intervention. This synthesis offers an integrated framework that connects cytokine signaling with clinical outcomes and provides guidance on subsequent standard, multi-omics studies to achieve precision immunomodulation and better disease prognostication.

INTRODUCTION

Parasitic diseases still act as a significant health burden to the world, especially in the tropics and subtropics, where malaria, leishmaniasis, trypanosomiasis, and schistosomiasis infections have remained a significant cause of morbidity and mortality despite decades of control measures [1]. The World Health Organization (2023) states that the number of new cases is millions each year, which highlights the potential of parasitic infection as a problem posing challenges to the health of humans, socioeconomic stability, and healthcare systems. These infections are characterized by intricate host-pathogen interactions whereby the immune system can be decisive on the outcome of the disease; total elimination of the parasite or chronic infection and immune-mediated pathology [2]. Cytokines are small, secreted signaling proteins that are among the immune components that mediate host defense as central regulators of immune and non-immune cell communication [3]. They regulate, strengthen immune responses, and are molecular switches that keep the balance between anti-inflammatory and pro-inflammatory responses in balance [4]. For example, T-helper 2 (Th2) cytokines, such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13), facilitate extracellular parasite expulsion but may also

DOI: https://doi.org/10.54393/fbt.v5i4.210

trigger allergic or fibrotic responses if dysregulated, while T-helper 1 (Th1) cytokines, such as interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α), and interleukin-12 (IL-12) [5]. On the other hand, anti-inflammatory cytokines such as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10) inhibit excessive inflammation, maintaining tissue integrity while also creating a niche for parasite persistence [6]. The action of cytokines through high-affinity receptors that activate intracellular signalling pathways like JAK-STAT, NF-κB, and MAPK. The stimulation of these pathways controls the expression of genes that manage the growth, differentiation, and activity of immune cells [7]. As an example, Th1 polarization and IFN-γ synthesis induced by IL-12 stimulation of STAT4, and Th2 polarization and antibody class switching signalling are induced by IL-4-stimulated STAT6. At the same time, TNF-α stimulates IL-1β the NF-κB, enhancing the transcription of inflammatory genes, whereas IL-10 and TGF-β involve inhibitory receptor stimulation to inhibit the expression of pro-inflammatory cytokine genes. Such organized molecular processes guarantee accurate immune regulation and maintain the balance between the destruction of pathogens and the protection of the tissues [8]. Available literature focuses on individual causal agents or cytokine families, and does not consider comparative dynamics, age-dependent changes, and chronic exposure outcomes. Thus, a new integrative paradigm is required to bridge the gap between cytokine signalling and clinical repercussions and potential therapeutic benefits. This study brings out the major functions of the cytokines, disease-specific profiles, and clinical implications of cytokine modulation. Altogether, the review provides a modern interpretation of cytokine networks that are associated with disease and the development of future immunomodulatory treatments.

This study aims to focus on the immune regulation of major parasitic infections through cytokine mediation in a systematic way by synthesizing the current molecular and immunological information.

The review was done in a structured and transparent manner in order to be comprehensive and reproducible. The process of the review was systematic literature identification, screening, and narrative synthesis of results as they applied to the understanding of cytokine-mediated immune responses in parasitic infections. PubMed, Scopus, and Web of Science databases were thoroughly searched, including the period between January 2010 and October 2025. Inclusion Criteria: The inclusion criteria were: 1. Original research or review articles in English, 2. Parasitic infections-reported cytokine profiles, immune modulation, or signaling mechanisms, and 3. Carried out in humans or tested in laboratory animal models. Exclusion Criteria: 1. Conference abstracts, cases, or non-peer-reviewed publications, 2. The literature that was devoid of cytokine-specific data, and 3. Duplicate data or unfinished data. Data Extraction: Full texts were checked to extract data, and eligibility was determined by title and abstract. The resulting information covered cytokine type, direction of regulation (up- or down-regulation), stage of infection, host species or age group, and disease outcome. To make sure that all figures used in this review are clear, accurate, and visually consistent, all of them were conceptualized and created with the help of Figma software.

Cytokines: Types and Functions in the Immune System

Cytokines are a general type of low-molecular-weight (usually 5-25 kDa) secreted proteins that are important intercellular messengers of the immune system [9]. They are mainly generated by immune cells (e.g., macrophages, dendritic cells, NK cells, T and B lymphocytes), although in many cases, non-immune cells (e.g., epithelial cells, fibroblasts) also contribute to their production [10]. Cytokines do so in autocrine, paracrine, and, less frequently, endocrine signals, interacting with high-affinity cognate receptors on their target cells and triggering intracellular signal transduction (notably JAK-STAT, NF-KB, and MAPK) and resulting in changes in gene expression, differentiation, proliferation, survival, and effector functions [11].

Classification of Cytokines: Type 1 vs Type 2 functional bias

Classification of Cytokines: Type 1 vs Type 2 functional bias was done (Figure 1).

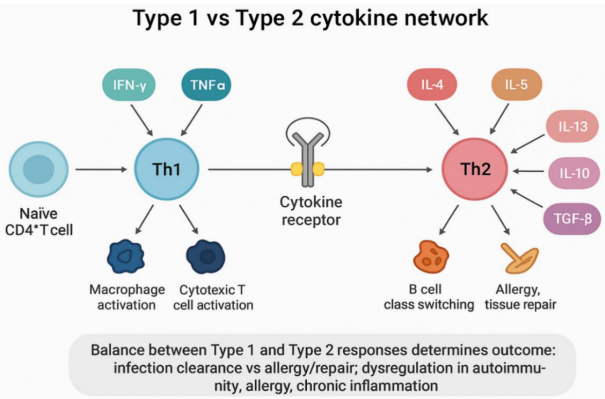

Figure 1: Type 1 versus Type 2 Cytokine Network in Immune Regulation

This schematic illustrates the differentiation and effector mechanisms of T-helper 1 (Th1) and T-helper 2 (Th2) immune responses. Th1 cytokines, including interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-12 (IL-12), promote macrophage activation and intracellular parasite clearance [12]. Conversely, Th2 cytokines, such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13), induce eosinophil recruitment, antibody class switching, and mucosal repair for extracellular parasite expulsion. The balance between Th1

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and Th2 responses determines infection outcomes, ranging from protective immunity to chronic inflammation and tissue fibrosis[13].

Functions of Cytokines

There are several fundamental functions of the immune system, cytokine-based, as follows(Figure 2):

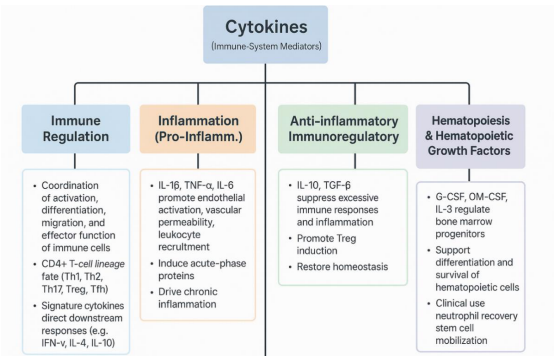

Figure 2: Functional Spectrum of Cytokine-Mediated Immune Responses

This diagram summarizes the principal functional categories of cytokines in host defense. Key functions include: (1) immune regulation (mediating activation)[14], differentiation, and communication among immune cells [15], (2) pro-inflammatory signaling, inducing acute-phase responses via IL-1β, IL-6, and TNF-α [16], (3) anti-inflammatory control, mediated by IL-10 and TGF-β to limit tissue damage [17], (4) hematopoietic support, through growth factors such as G-CSF that promote bone marrow cell proliferation [18]. Together, these interconnected cytokine pathways orchestrate host immunity, homeostasis, and pathogen tolerance.

Cytokine Mechanisms in Parasitic Infections and Host Immune Response

Cytokines are the major signalling molecules that coordinate immune responses to parasitic infections, as they serve as molecular messengers connecting innate and adaptive immunity. Parasitic pathologies: the presence of helminthic (multicellular parasites) and protozoan (unicellular parasites) parasites induces a very different cytokine profile, resembling the character of the infecting pathogen and the type of effector response needed to control it [19]. Pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), and NOD-like receptors (NLRs), are recognized by innate immune cells at the onset of infection, macrophages, dendritic cells (DCs), and epithelial cells. It leads to the release of pro-inflammatory cytokines (IL-1β, IL-6, TNF-alpha, and IL-12) and chemokines that determine the inflammatory milieu, which predetermines future adaptive reactions[20].

- Cd4 + T-cell differentiation into specialized subsets is determined by the cytokine microenvironment[21].
- Th1: IL-12 and IFN-γ trigger the program of Th1 to induce the killing of protozoa within the cell by macrophages[22].
- Th2 cells, which are induced by epithelial-derived alarmins including IL-25, IL-33, and TSLP, trigger eosinophil recruitment and antibody (IgE) generation needed to expel helminth[19].
- Tregs (regulatory Tregs) are cells that reduce overproduction of inflammation induced by the effects of IL-10 and TGF-β and control tissue damage [23].
- IL-6, IL-21, and IL-23 regulate Th17 cells that perform the functions of mucosal protection and granulocyte mobilization and may also cause immunopathology in chronic infections[24].

Helminth Infections: Th2 and Regulatory Dominance

Nematodes, trematodes, and cestodes cause helminth infections, which are characterized by a Type 2 immune response. Such an IL-4-driven cytokine environment orchestrates the mobilization of effector cells, eosinophils, mast cells, basophils, and alternatively activated macrophages (M2)[25]. It involves IL-4 and IL-13 that promote B-cell class switching to IgE, mucus secretion, and intestinal smooth muscle contractility, which is a physical elimination mechanism, the so-called weep and sweep response[26].

- The IL-5 attracts and stimulates eosinophils, which contain cytotoxic granules (major basic protein, eosinophil cationic protein) that destroy helminth cuticles[27].
- The IL-33, which is discharged as an alarm by necrotic cells of the epithelial and endothelial layers, enhances Th2 polarization through the stimulation of innate lymphoid cells type 2 (ILC2s), which increase the production of IL-5 and IL-13[28].
- The secretion of IL-27 by macrophages and dendritic cells has a modulatory effect, which increases Th1 responses but subsequently stimulates the secretion of IL-10, thereby limiting Th2-mediated pathology [29].

Protozoan Infections: Th1-Driven Immunity and Pathology

Protozoan parasites, including Plasmodium, Leishmania, Toxoplasma gondii, and Trypanosoma spp., are mostly located inside host cells, which requires a Th1-biased response to be controlled successfully[30].

- NK cells and Th1 differentiate and produce strong amounts of IFN-γ in response to IL-12 released by antigen-presenting cells[31].
- IFN-γ causes classical macrophage activation (M1 phenotype), which increases inducible nitric oxide synthase (iNOS) and reactive oxygen intermediates (ROI) involved in intracellular killing of parasites[32].
- TNF-alpha, acting synergistically with IFN-γ, potentiates phagolysosome fusion and increases MHC expression, which reinforces antigen

DOI: https://doi.org/10.54393/fbt.v5i4.210

presentation [33].

Although these cytokines are necessary in the regulation of the replication of protozoans, when overactivated or prolonged, Th1 may lead to immunopathology. An example is that high levels of IFN-γ and TNF-α are involved in the inflammation of the brain of the Plasmodium falciparum malaria [34] and the hepatic granulomas of the Leishmania donovani infection [35]. A regulatory feedback mechanism develops in chronic protozoan infection. IL-10, IL-27, and TGF-β reduce hyperinflammation, which protects host tissues; however, unintentionally, it facilitates persistence of the parasite [36].

Cytokine Profiles in Malaria Diseases

Recent quantitative studies have shown that there are specific cytokine concentration gradients that reflect the severity of malaria and the outcome of the immune response. TNF-alpha (TNF-α) concentrations usually lie within 45 -120 pg/mL-1 in non-complicated infection, and up to 200 pg/mL-1 in complicated or cerebral malaria, which is why it has been proposed as a primary mediator of endothelial activation and inflammation in Plasmodium falciparum infection [34, 37]. Likewise, interferon-gamma (IFN-γ) levels rise to 30-80 pg/mL-1 in mild disease and 150-200 pg/mL-1 in advanced infection, as a result of hyperactivation of the macrophages and the production of nitric oxide [38]. However, regulatory cytokine interleukin-10 (IL-10), on the other hand, increases substantially in the case of acute infection (60-110 pg/mL-1) as a response to inflammation, but overproduction of IL-10 leads to parasite survival and chronic infection [39]. Multi-cohort meta-analysis by [40] and recent systematic reviews [41] confirm that a high TNF-α/IL-10 ratio (> 2.5) is a strong predictor of severe or fatal malaria, whereas a balanced ratio is strongly associated with controlled parasitemia and improved survival. Overall, these results indicate that the malaria immunopathology is mediated by cytokine imbalance and not cytokine abundance, and highlight the therapeutic role of cytokine signaling pathways modulation in the disease.

Leishmaniasis

Based on human research, local and systemic immune conditions are differentially characterized by quantitative cytokine signatures of cutaneous (CL) and visceral leishmaniasis (VL). In visceral leishmaniasis, IL-10 in circulation is always high before therapy (mean values at reported level of about 4664 pg/mL-1), and drops significantly upon effective therapy, which indicates it to be an active disease and immunosuppressive marker [42, 43]. Simultaneously, systemically IFN-γ can be detected in VL but at lower systemic concentrations than in localized CL; IFN-γ responsiveness can be restored by treatment and is associated with clinical cure. In the case of cutaneous leishmaniasis, the local (lesional) and PBMC-stimulated cytokine levels depict the presence of far more IFN-γ production: Peripheral blood mononuclear cell (PBMC) cultures often have median IFN-γ -844 pgmL-1 (range 198-1753 pgmL-1), lesion culture supernatants report lower yet significant values (median -271 pgmL-1, range 0-758 pgmL-1), indicating strong local Th1 response [44]. In CL, IL-10 is not fixed across cohorts, but may rise to levels of 60-150 pg/mL-1 in serum or lesion fluid in various recent studies, with higher IL-10 being consistent with poor parasite killing or chronic lesions [45]. TNF-α and IL-12 are usually moderate (tens to low hundreds pgmL-1) and cooperate to activate protective macrophages in controlled disease, but overproduction of local TNF-α still leads to tissue pathology. The IFN-γ/IL-10 ratio has been reported as a clinically useful index to differentiate between healing and progressive disease (higher ratios support parasite control), and persistent high levels of IL-10 (low IFN-γ activity) are associated with treatment failure or chronicity. These quantitative trends, combined with each other, support the idea that the balance and the compartmentalization of cytokine responses (local lesion vs systemic circulation) and not individual absolute values control leishmaniasis outcome and the need to use IL-10 and IFN-γ as translational biomarkers in clinical research.

African Trypanosomiasis

Stage-dependent cytokine signatures of human African trypanosomiasis are reproduced: an initial systemic pro-inflammatory response (high IFN-γ, TNF-α, IL-6) and a consequent late response shift to strong regulatory/neuroinflammatory reactions (significant IL-10, CSF cytokine responses). Cohort studies in peripheral blood show that the median IFN-γ values are in the range of 30-75 pg/mL-1 to 40-130 pg/mL-1 in the blood of the systemic macrophage and the T-cell in the peripheral blood cell samples in the hemolymphatic stage [46]. To CNS progression, there were significant rises in IL-10 and IL-6 [47] (rhodesiense cohorts) in late-stage patients (CSF IL-10 and IL-6 levels often many times higher than those peripherally and often high-to-hundreds pg/mL-1), which is a symptom of neuroinflammatory action and CSF staging [47]. Significantly more than equivalent malaria cases and healthy controls, rhodesiense HAT cohorts had median plasma cytokine concentrations of about IFN-γ, 72.2 pg/mL-1, IL-6 55.0 pg/mL-1, and IL-10 115.5 pg/mL-1, highlighting the strong systemic inflammation in HAT [46]. Relative changes and compartmentalization (blood to CSF), e.g., a decreasing IFN-γ/ IL-10 ratio and increasing CSF IL-6/ IL-10, are more powerful predictors of CNS progression and poor neurological outcome than any single cytokine concentration, pointed out by meta-analytical and review syntheses. These quantity patterns are behavioural at the stage, making it possible to employ specific combinations of cytokines (IFN-γ, IL-6, IL-10, TNF-α) to enhance staging and prognostication [48].

Schistosomiasis

Schistosomiasis has a unique immunological progression

DOI: https://doi.org/10.54393/fbt.v5i4.210

of an early Th1-dominated inflammation to a chronic Th2-dominated and regulatory cytokine response, which supports the development of granuloma and hepatic fibrosis. Quantitative studies have shown that the infection of Schistosoma mansoni induces high IL-4, IL-5, and IL-13 responses, which are associated with deposition of eggs, and IL-10 and TGF-β, which inhibit immunopathology [49]. The level of IL-13 in serum and Schistosoma egg-antigen (SEA)-stimulated cultures in chronic hepatosplenic cases is frequently higher than 1,000-1500 pg/mL-1, whereas in mild or intestinal cases, the concentration of IL-13 is 300-600 pg/mL-1 [50]. In controlled disease, IL-10 is normally 60-120 pg/mL-1, whereas in patients with advanced fibrosis, it is lower than 50 pg/mL-1, hence loss of immunoregulation [49]. The IL-6 and TNF-α, which reach their peaks during the acute infection (70-180 pg/mL-1 and 50-150 pg/mL-1, respectively), also decrease and are replaced by the Th2 and regulatory cytokines [51]. Taken together, these facts indicate that the morbidity of schistosomiasis is caused by the imbalance between cytokine, i.e., fibrogenesis under the influence of IL-13, and the insufficiency of control by the cytokine IL-10, rather than the abundance of any of the cytokines.

Synthesis and Insights

The current review highlights the key importance of cytokines in the coordination of immune responses to parasitic infection, which is that the outcome of diseases is not necessarily determined by the magnitude of cytokines individually, but rather by the dynamics between pro-inflammatory cytokines, anti-inflammatory cytokines, and regulatory cytokines. In malaria, leishmaniasis, trypanosomiasis, and schistosomiasis, quantitative and comparative synthesis has shown that relative disregard of cytokine balance produces parasite persistence and host pathology, and is not a result of relative over-or under-production. TNF-α, IL-6, and IFN-γ levels of patients with Plasmodium infections are positively associated with severe or cerebral malaria, and counter-regulatory IL-10 can stop excessive inflammation but allow chronic parasitemia. Ratios of similar cytokines (TNF-α/IL-10 > 2.5) have been suggested to be predictors of the severity of the disease [34, 40]. Similar duality is present in the case of Leishmania infection, whereby IFN-γ and IL-12 stimulate macrophage activation and parasite elimination, and high levels of IL-10 and IL-4 promote the persistence and chronic cutaneous lesions. Results of quantitative human studies testify to this ratio: the average IFN-γ concentrations in the cutaneous disease are often higher than 800 pg/mL-1, and the concentration of IL-10 above 100 pg/mL-1 is associated with poor response to therapy [44, 45]. Cytokine patterns of African trypanosomiasis change with time, whereby initial stages are dominated by IFN-γ, which is replaced by TNF-α dominance and then IL-6/IL-10 dominance in suppressing the immune system and inflammatory reactions on the central nervous system, respectively. Cerebral IL-10 (>200 pg/mL-1) and IL-6 (>120 pg/mL-1) are confirmed as late biomarkers [46, 47]. It is supported by these findings that disease progression is also characterized by compartmental redistribution of cytokines, especially in the CNS, which contributes to immune depletion and neurological pathophysiology. Cytokine dynamics in the case of schistosomiasis are characterized by a change towards Th2 and profibrotic. High IL-13 (>1 mg/mL-1) is related to hepatic fibrosis, and low IL-10 (<60 pg/mL-1) impairs immunological control and enables the development of granulomatous inflammation [50]. The IL-13/IL-10 ratio, therefore, can be considered a useful measure of fibrogenic potential in line with the TNF-α/IL-10 ratio applied in malaria prognosis. Collectively, these disease-specific cytokine ratios represent a general immunoregulatory paradigm in parasitic infections: pathology is caused by uncoupled pro-inflammatory and regulatory cytokines either temporally or in intensity. In comparison, this synthesis shows that there is a common immunological rationale: parasites take advantage of host regulatory mechanisms to play safe without inducing sterilizing immunity. Protozoan and helminth parasites use recurrent cytokine mimicry, receptor modulation, and intracellular signalling interference (e.g., JAK-STAT, NF-κB, and MAPK pathways). Modern transcriptomic studies also indicate that persistent IL-10 and TGF-β signalling of chronic infections reprograms immune-metabolic responses to facilitate tolerance and suppress effector exhaustion [52]. Controlled cytokine modulation is a promising therapeutic approach in the reduction of immunopathology that should not cause the weakening of host defense. In malaria and leishmaniasis, adjunctive therapy using anti-TNF-α or IL-6 signaling has been demonstrated in experimental studies to minimize tissue damage without suppressing antiparasitic immunity. Equally, antifibrotic effects of IL-13 or downstream fibrotic mediators (e.g., TGF-β and collagen production) inhibition have also been seen in schistosomiasis models [51]. Nonetheless, the differences in the host responses, which depend on genetic, environmental, and co-infection factors, predetermine the need to use individual or population-specific immunotherapeutic methods. Even with the tremendous improvements, there are still a number of gaps. Most cytokine research uses cross-sectional data or induced culture, which does not provide an understanding of the kinetics in vivo. Similarity of cytokine measurements and assays requires standardization of cytokine measurements and assay platforms to achieve meta-analytic consistency. In addition, combined with transcriptomic and metabolomic data, cytokine profiling may be investigated in multi-omics to understand regulatory feedback mechanisms that can control the results of infections.

DOI: https://doi.org/10.54393/fbt.v5i4.210

CONCLUSION

This review highlights how cytokine-mediated regulation is the concept defining immune outcomes during parasitic infections. The comparative analysis of malaria, leishmaniasis, trypanosomiasis, and schistosomiasis indicates that the severity and persistence of the disease are not caused by the presence of cytokines but rather by the imbalance of cytokines - especially in ratios like TNF-α/ IL-10 and IL-13/ IL-10. Further quantitative data demonstrate that parasites manipulate host cytokine networks in a strategic manner using JAK-STAT, NF-κB, and MAPK signaling pathways to develop chronic infection and immune tolerance. These results offer an integrated paradigm of cytokine signaling in host-parasite interactions, pathogenesis, and therapeutic possibilities. Further studies are required to focus on standardized cytokine measurements, longitudinal multi-omic combination, and cytokine-based immunomodulation in order to enhance diagnostic accuracy and clinical prognosis in parasitic infection.

Authors Contribution

Conceptualization: MS
Methodology: MS, AW, AR, SF, SH
Formal analysis: MS
Writing review and editing: MS, AW, AR, ZW, SF, SA, AAK

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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