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The sustainable role of parasites in modulating environment, immune system and gut microbiota

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Abstract

Parasites are known as detrimental organism due to their adverse effects on human and animal health. However, besides negative effects, they play critical roles in various ecological and physiological processes. For example, they serve as bio accumulators that help control pollution. Cestodes such as *Paraotigmatobothrium* and *Anthrobothrium* species carry high levels of lead and cadmium than the tissues of their host fish. Recent researches have revealed that parasites present in fish species like *Oreochromis niloticus*, *Parachanna obscura*, and *Clarias gariepinus* are capable of accumulating higher levels of heavy metals which affects the overall burden in aquatic system. On the other hand, parasites plays significant role in the modulation of immune system by various pathways. Anti-inflammatory protein-2 (AIP-2) is a hookworm protein which is responsible for expansion of regulatory T cells (Tregs), resulting in reduction of inflammation in animal models of colitis. Similarly, Transforming Growth Factor-β mimic (TGM) obtained from *Heligmosomoides polygyrus* Tregs by binding with TGF-β receptors (TGFβR). Both TGFβR-I and TGFβR-II receptor chains can independently and firmly bind to TGM. But TGF-β directly binds with TGFβR-II chain, which then phosphorylates TGFβR-I. Another example is P53, a *Trichuris muris* derived protein, which plays a significant role in suppression of type 2 immune responses by trapping interleukin-13 (IL-13) in extracellular matrix. This trapping of cytokine is facilitated by thrombospondin-like binding motif present in p53. Helminths play a significant therapeutic role in autoimmune disorders, such as alleviation of multiple sclerosis and ulcerative colitis by regulating immune responses. A study in Argentina revealed that gastrointestinal helminth infection causes high levels of IL-10 and TGF-β resulting suppression of multiple sclerosis. Similarly, experimental infection with *Trichuris trichiura* has alleviated the symptoms of ulcerative colitis. Parasites also have the potential to alter the host gut physiology and microbial dynamics. The physiological processes like cell proliferation, apoptosis, and cell activity are influenced by the presence of *Trichuris* in large intestine. Furthermore, certain species of protozoa have significant effect on gut health and microbial balance by altering the Firmicutes-to-Bacteriodetes ratio. Parasites are necessary for one health by playing crucial role in supporting environment and animal and human health, yet in moderate concentration.

1. Introduction

Parasites, especially helminths, are well known for their notorious role in disturbing economy by damaging agriculture and public health (Ur-Rehman et al. 2023). Haemoparasities and ectoparasites are leading contributors to various diseases in humans and animals, such as tick-born disease, babesiosis, Hendra, Ebola, Nipah, and SARS-CoV (Küçükyağlıoğlu and Uslu 2024; Nadeem et al. 2024; Zheng et al. 2024). Most parasites act as vectors for various zoonotic pathogens and hence, pose a significant threat to public health (Baz et al. 2024). Various species of parasites are generally considered as harmful for ruminants, poultry, equines, humans, and environment. However, there is limited research on the beneficial role of parasites in regulating public health and economy of a country. In this aspect, parasites resemble microorganisms by exerting both beneficial and harmful effects. Parasites positively affect the host health by regulating gut microbiota and immune system. Moreover, parasites are also called as "old and dirty" creatures, playing their friendly role in protecting environment, particularly by mediating pollution control. In ecological systems, parasites constitute a fundamental portion of natural ecosystems, whereby they act as agents of natural selection and affect the constitution of communities of free-living organism (Gómez and

Nichols 2013; Poulin 1999; Solórzano-García and Pérez-Ponce de León 2018). They are also important for the ecological interaction of their hosts, such as mutualism and commensalism, hence are commonly found in plant and animal populations (Gilbert 2002). Parasites help maintain gut microbial and immune balance of host. They favourably regulate the immune responses associated with various autoimmune diseases induced due to the inflammatory responses in host (De Ruiter et al. 2017; Smallwood et al. 2017). By modulating immune signaling parasites control the inflammatory responses and protect their host (Maizels 2020). The presence of protozoa and helminths may alter the composition of gut microbiome to improve its functionality. However, there are significant adverse effects of parasites, such as ecto-parasites spread diseases either by direct bites or act as carrier of other pathogens, like arboviruses and tick-borne infections; and endo-parasites directly invade the internal organs of body like intestines, muscles, lungs, liver, and blood, thereby causing systemic dysfunction and significant economic losses (Shah and Khan 2019).

2. Beneficial aspects of parasites

2.1. Impact on pollution

Certain parasites have an exceptional capacity to accumulate pollutants from their host, such as certain endo-parasites have ability to concentrate inorganic elements, such as heavy metals, at levels far higher than free-living species. Hence, they are considered as valuable bioindicators of environmental pollution and have been used as bioaccumulation indicators in aquatic and terrestrial ecosystems (Nachev and Sures 2016). In order to serve as reliable bioaccumulation indicators, parasites must meet following criteria (Vidal-Martínez and Wunderlich 2017):

(1). They should have a high potential to accumulate pollutants while being tolerant to their effect

(2). They should be common, abundant, and easily recognizable in a given ecosystem

(3). They should be large enough to provide sufficient tissue for chemical analyses

(4). They should be stationary or have a confined home range to ensure localization of pollutant detection.

2.1.1. Cestoda parasites: Indicators of heavy metal contamination

The potential for bioaccumulation of various heavy metals like lead, iron, and zinc is significantly higher in a marine fish infected with Cestoda parasites (Hassan et al. 2018), making these parasites reliable biological indicator of heavy metal contamination. For example, *Paraotigmatobothrium* and *Anthrobothrium* species exhibited higher concentrations of lead and cadmium than the gonads, liver, and kidneys of sharks from Iranian coast (Malek et al. 2007). These observations assert the hypothesis that helminth parasites serve as sensitive early-warning bio-indicators of low-level heavy metal environmental hazards.

2.1.2. Bioaccumulation of heavy metals in Clarias gariepinus and Parachanna obscura

A study of Lekki lagoon, Nigeria, revealed that intestinal nematodes of *Clarias gariepinus* and *Parachanna obscura* accumulated higher levels of heavy metals like copper, iron, chromium, lead, and nickel compared to tissues of fish (Bamidele and Kuton 2016). Other studies have demonstrated the ability of parasites to detect shifts in chemical condition of the water, which makes them valuable tools for monitoring heavy metal pollution of both saltwater and freshwater (Mehana et al. 2020; Sures 2001).

2.1.3. Oreochromis niloticus: Bio indicators of heavy metal pollution

In some lakes of Egypt, such as Mariout, Edku, and Edfina, *Oreochromis niloticus* commonly infected with parasites such as Trematodes, Monogenea, Protozoa, Crustacea, and Acanthocephala, which are associated with the higher concentration of the heavy metals such as lead and cadmium in the host fish (Ashmawy et al. 2018). An interesting observation is that the concentrations of heavy metals including copper, cadmium, lead, and Zinc were low in cattle infected with *Dicrocoelium lanceatum* and *Fasciola hepatica*. The extent of reduction corresponded with the intensity of parasitic infection. This is believed to be attributed to the fact that the helminths have the capability of sequestrating and storing these metals within their own bodies, thereby reducing their levels in the body organs and circulatory system of the host. The binding of metals by over 251 helminthic species can be viewed as a form of defense to the host by lowering the toxic heavy metal storage and also as a metabolic requirement for trace element by the parasites. These facts highlight the unexplored ecological role of parasites in regulating the metal homeostasis of their hosts and suggest potential implications for animal health and environmental toxicology (Khovidhunkit et al. 2004).

2.2. Impact on immune system

Parasites play vital role in immune modulation. Regulatory T cells (Tregs) are well known for their regulatory role in immune tolerance by being directly stimulated by parasites (Maizels and Smith 2011). In order to exploit the Treg pathway, parasites have developed a number of tactics, such as manipulation of Dendritic Cells to promote IL-10 production (Navarro et al. 2016; Zaccone et al. 2009) and Treg induction. Furthermore, the pathways involving immunosuppressive macrophages and regulatory B cells (Bregs) have been linked to the helminth-mediated immune regulation (Correale et al. 2008; Hussaarts et al. 2011).

2.2.1. Role of parasites in immune modulation

A recent study has revealed that Anti-Inflammatory Protein (AIP)-2 secreted by hookworm plays a vital role in expanding Tregs by acting through CD^{103+} dendritic cells in animal models and has significantly reduced the colitis induced by Trinitrobenzene sulfonic acid administration as well as allergic airway inflammation (Ferreira et al. 2017). Similarly, *Heligmosomoides polygyrus* also secretes a Transforming Growth Factor- B mimic (TGF- M) which despite its genetic variations from mammalian TGF-β can also recognise TGF-β receptors. This contact triggers Smad phosphorylation and Foxp3 expression in T cells and thus enhances Tregs differentiation. These helminth-derived molecules promote the growth of Tregs and suppress the effects of a pro-inflammatory response, thereby employing an anti-inflammatory environment conducive to parasite survival whilst potentially decreasing host pathology resulting in immunotherapy of the host (Gazzinelli-Guimaraes and Nutman 2018; Johnston et al. 2017). TGF-M, however, is secreted as a full-length active protein, unlike host-derived TGF-β, which cannot be released without the proteolytic cleavage by extra-cellular integrin matrices for activation. This enables the parasites to circumvent host-dependent activation mechanism and directly induces immunoregulatory effects. A second functional difference is that TGF-β first binds to the TGF-β receptor II and subsequently

recruits receptor I, TGF-M exhibits dual-specific binding to both receptor chains independently, albeit with lower individual affinity. By enhancing dual-specific binding to each of the receptor chains, TGF-M reinforces a stronger and effective activation of the TGF-β signaling pathway, and thus strongly inducing Foxp3 expression and Treg differentiation. These features of *H. polygyrus* modulate the host immune responses and illustrate how the core host-parasite evolutionary adaptions allow the parasite to maintain long-term persistence within the host. As a result, TGF-M can induce Foxp3 expression in naive T cells, thereby ascertaining as a functional ligand within the TGF-β signalling pathway. The induction and activation of Tregs by *H. polygyrus* are the primary mechanism against competent immune hosts, whereby they reduce excessive inflammatory reactions, that would otherwise lead to the elimination of the parasite. Thus, TGF-M is a major molecular pathway through which *H. polygyrus* induces Treg differentiation and immune tolerance (Smith et al. 2016). It has also been demonstrated that remarkably, TGF-M can extend the survival of skin grafts in mice that have genetically mismatched donors, a result comparable to complete parasite infection. Fig. 1 summarizes the role of TGM in the immune modulation. Another immunomodulatory mechanism is mediated by protein p53, which is secreted by *Trichuris muris* and interferes with host cytokine network. This protein has a separate thrombospondin resembling binding site which facilitates its binding with host IL-13 and induces suppression of type 2 immune responses (Bancroft et al. 2019). In allergic asthma, IL-13 plays a significant role in its progression, which underscores the potential of human whipworm *T. trichiura* derived proteins to reduce its severity (Maizels 2020).

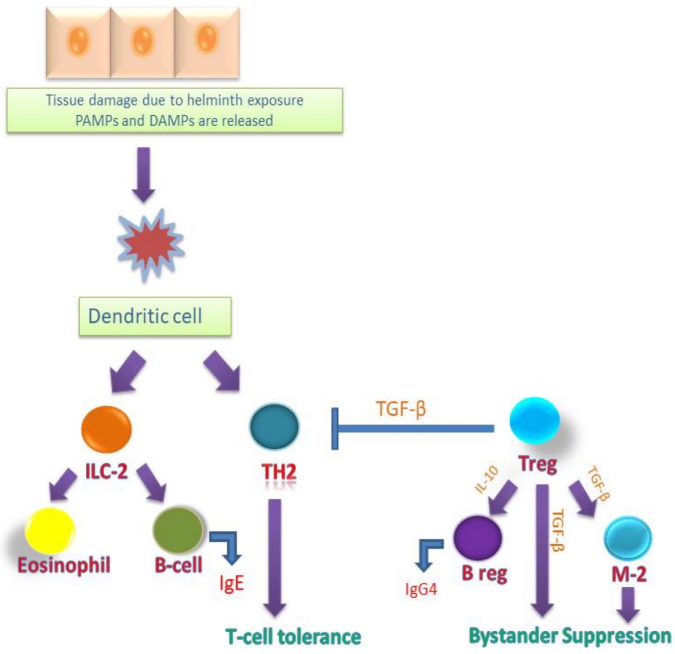

Fig. 1. *Routes of immunological regulation by helminths and allergic inflammation (Maizels 2020)*

2.2.2. Helminths in the treatment of autoimmune disorders: A case study of MS patients in Argentina

Several studies have demonstrated significant role of helminths in treating autoimmune disorders. An intriguing study in Argentina revealed that multiple sclerosis (MS) patients, who unintentionally got gastrointestinal helminth infections, remained in remission for more than four years compared to uninfected MS patients with similar severity levels at the beginning who experienced varying degrees of relapse (Correale and Farez 2007). The immunological analysis of infected individuals revealed decreased levels of inflammatory cytokines, along with increased levels of TGF-β and IL-10, and a larger Bregs compartment (Correale et al. 2008). The remission of MS persisted until the sixth year except in four patients who received anthelmintic treatment where disease symptoms reappeared, along with reduction in TGF-β and IL-10 levels (Correale and Farez 2011).

2.2.3. Helminth therapy for Ulcerative colitis: Impact on immune response and gut health

Helminth-based therapy has also shown potential in treating ulcerative colitis, a severe form of inflammatory bowel disease (IBD). *Trichuris trichiura*, one of the least pathogenic intestinal helminths in humans, has demonstrated immunoregulatory properties in clinical cases. In a remarkable self-infection case study, a patient who administered *T. trichiura* eggs to themselves experienced a reduction in clinical symptoms. Biopsy specimens revealed a decline in inflammatory Th17 subsets and an increase in Th2 cells expressing IL-4, as well as Th22 subsets producing IL-22 (Broadhurst et al. 2010). Moreover, goblet cell-derived mucus secretion significantly increased following infection, promoting epithelial protection. Collectively, these findings suggest that helminths alleviate ulcerative colitis by (i) reducing inflammatory T cell activity, (ii) enhancing barrier function, (iii) inducing tissue regeneration via IL-22, and (iv) driving mucus responses through type 2 cytokines such as IL-4 and IL-13 (Maizels 2016).

2.3. Impact on digestive system

2.3.1. Helminthology and gut health

2.3.1.1 Trichuris specie in cell proliferation and apoptosis

Trichuris species is widespread in both animals (ruminant and rodents) and humans with crucial effects on apoptosis in hosts. In humans, *T. trichiura* causes trichuriasis, commonly presenting mild symptoms and occasional anemia, abdominal pain, and chronic diarrhea. Recent studies have reported that chronic *T. muris* infection in mice induced increased cell proliferation and apoptosis in the large intestine, particularly at the base of crypts. Severe infections have increased the rate of proliferation of cells in the distal regions of the crypts as well. However, such infection did not influence rate of proliferation and apoptosis in the small intestine, though visible structural changes were observed (Hayes et al. 2017; Kapczuk et al. 2020). Due to poor hygiene and socioeconomic factors, developing countries are facing widespread helminth infections. Intestinal helminths alter gut microbiota structure, which affect the gut physiology, permeability, and mucus secretions. Some helminths produce antibacterial secretions, while others prevent harmful bacterial colonization, which indirectly reduce risk of adenocarcinomas (Grainger et al. 2013).

2.3.1.2. Bacteria-helminth relationship in Gut

The interaction between gut bacteria and helminths is beneficial for maintaining gut health in various ways. For example, the progression of *Lactobacillus* species is enhanced by *H. polygyrus*, a mouse duodenal parasite. Their interaction helps promote immune responses, control inflammation, and regulate gut mucosal health. Moreover, it protects from colitis and improves epithelial barrier functions (Su et al. 2011).

Conversely, antagonistic interactions may also exist, where some helminths indirectly reduce beneficial Lactobacillus populations, potentially contributing to pathological outcomes such as sepsis (Sędzikowska and Szablewski 2021). Thus, the relationship between helminths and host microbiota can be both protective and harmful, depending on the species involved.

2.3.1.3. Helminth induced regulation of bacterial diversity

Parasites may induce selective changes in gut microbial communities to maintain immune and intestinal balance. For example, *Enterobius vermicularis* infection results in high levels of *Bifidobacterium longum* and *Faecalibacterium prausnitzii*, while decreasing members of *Fusobacteria* phylum in children. Similarly, *Actinobacteria* phylum and *Streptococcus thermophiles* are favoured at the cost of *Fusobacteria* phylum, particularly *Fusobacterium varium*, on exposure of *E. vermicularis* combined with Mebendazole treatment (Yang et al. 2017). Similarly, *Ascaris* species exert complex effects on gut microbiota due to their intra and extra intestinal migratory behaviors, whereby they cause infection in multiple organs (Deng et al. 2021). *Ascaris suum* infection has been reported to alter gut bacterial diversity by favouring *Turicibacter* and *Succini vibrio* populations and decreasing *Lactobacillus*, thereby improving gut health (Cooper et al. 2013; Rosa et al. 2018). Based on their behavior, parasites can influence the gut microbiota either directly or indirectly. This effect may occur in a generalized manner, by increasing the overall diversity and abundance of microbial populations, or in a microbe-specific way, targeting particular groups such as bacteria or protozoa. For instance, in children co-infected with *Trichuris trichiura* and *Ascaris lumbricoides*, treatment directed specifically against *T. trichiura* did not produce significant alterations in the intestinal microbiota composition. However, infections with *T. trichiura*, hookworms (*Ancylostoma* and *Necator*), and *A. lumbricoides* have been associated with modifications in the average diversity and structure of gut bacteriophage communities.

2.3.2. Gut health and protozoa

Several protozoa are the integral part of intestinal microbiota, such as *Blastocystis* species, *Entamoeba histolytica, Toxoplasma gondii*, and *Cryptosporidium* specie (Burgess et al. 2017).

2.3.2.1. Blastocystis and Firmicutes/Bacteroidetes ratio

Blastocystis is a common protozoan, inhibiting the gut of both animals and humans, usually transmitted through oro-fecal route. Though, commonly associated with irritable bowel syndrome and resistance to ulcerative colitis treatment (Nourrisson et al. 2021), *blastocystis* can play beneficial role in gut microbial balance. Dysbiosis, defined as imbalance in composition of gut microbiota often measured by the Firmicutes/ Bacteroidetes ratio (F/B ratio), indicates complications like IBD. *Blastocystis* plays a significant role in combating various metabolic disorders by lowering F/B ratio (Yañez et al. 2021). In Colombian schoolchildren, *Blastocystis* infection resulted in high levels of *Faecalibacterium* and reduced levels of *Bacteroides and Prevotella*, which fostered the developing anti-inflammatory environment in human gut and helped in prevention of IBD conditions (Castañeda et al. 2020).

2.3.2.2. Variations in Entamoeba species: E. histolytica vs E. dispar

Parasites within the same genus may vary in pathogenic potential and accordingly affect the bacterial diversity in gut. For example, *E. histolytica*, a pathogen, causes higher levels of Firmicutes and lower levels of Bacteroidetes, whereby the subsequent interaction between microbiota and *E. histolytica* may enhance parasitic virulence and trigger host inflammation. On the hand, *E. dispar*, a nonpathogen, is linked to increased bacterial diversity with reduced Bacteroides level (Even et al. 2021).

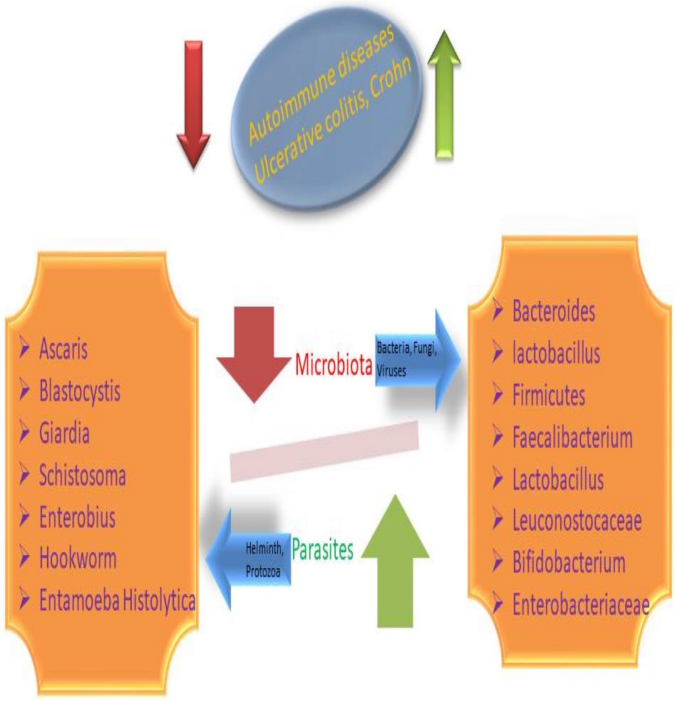

Fig. 2. *The balance between microbiota and parasites (Beyhan and Yıldız 2023)*

3. Future perspectives

The physiologically important parts of the gut are inhabited by microbiota, such as bacteria, nematodes, and protozoan parasites, which have co-evolved with their host over thousands of years, jointly contributing to complex ecological and immunological interactions. Though factors such as altered diet and stress disrupt gut microbial balance, leading to chronic diseases (Ipci et al. 2017), emerging research shows that dysbiosis may arise through shifts in microbial abundance, metabolic changes, or alterations in community structure. The dysbiosis has been associated with *Clostridium difficile* infection, Crohn's disease, and ulcerative colitis. The tailored treatment with blastocystis used as a probiotic restores the balance and reduce gut inflammation (Gil et al. 2016). Research studying the relationship between gut microbes, protozoa, and the host immune system has led to a blossoming of new treatment avenues, such as probiotics, prebiotics, and fecal transplantation, which are set to become central to the management of gut infection and inflammation (Partida-Rodríguez et al. 2017).

Therefore, modulation of the microbiota through probiotics, prebiotics, and fecal transplants is a promising treatment strategy to prevent the establishment of parasitic infections as well as to treat disorders such as allergies, IBD, and autoimmune diseases. Such interventions may be useful in diseases caused by protozoal pathogens like *E. histolytica*, *Giardia duodenalis*, *Cryptosporidium*, and *Toxoplasma* (Ipci et al. 2017). This modulation in gut could alter the interactions between the bacteria and between the bacteria and other protozoa, thereby tipping the balance toward or against disease. However, further

research is needed to unravel these interactions using specific animal models such as germ-free organisms, which will help understand how an imbalance in gut microbiota causes diseases. Helminths are very powerful mediators of the type 1 immune responses by counteracting inflammation and/or autoimmune pathology. However, current research aims at elucidating the molecular mechanisms through which helminths regulate immunity and identify potential molecular targets to overcome allergic, autoimmune, or metabolic disorders (Gazzinelli-Guimaraes and Nutman 2018). The contribution of helminths to the regulation of disease susceptibility should be carefully considered in future studies on helminth infections. While genetic factors of susceptibility in small groups of study populations are emphasized in biomedical research, helminth-induced granuloma infections underscore the role played by host responses other than their genotype in instigating the pathogenic effects of infections (Ebrahimiyan et al. 2019; Jia et al. 2017; Sun et al. 2017; Zhou and Haina 2017). It may be that environmental conditions, functional homeostasis, gut microbiota structure, and host physiology can shape the variations in vulnerability of individuals with similar genetic history to the same illness (Smallwood et al. 2017). Investigating how these variables interact with helminths will open up new directions in the course of disease prevention and treatment.

5. Conclusion

Parasites play a complex but significant roles in ecology as well as in human and animal health. While frequently associated with diseases, they contribute positively to environmental sustainability as bioindicators and heavy-metal accumulators, thereby helping to monitor and mitigate pollution. Helminths, in particular, have emerged as key regulators of immune balance, with therapeutic potential against autoimmune diseases such as multiple sclerosis and ulcerative colitis. They also play indispensable roles in gut homeostasis, regulating microbiota composition, enhancing mucosal defense, and reducing inflammatory responses. Taken together, parasites should not only be viewed as detrimental pathogens but also as vital ecological and physiological partners with promising applications in medicine and environmental sciences.

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