Review

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Microbiota-Parasite Interaction: Implication of Secretory Immunoglobulin A and P2X7 Receptor Signaling

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The microbiota community is composed of bacteria, fungi, viruses, and protists that exert symbiotic effects within the human body. Unlike microbiota, parasites are characteristically reliant on their hosts to thrive and flourish, producing toxic metabolites that agitate microbiota and disturb homeostasis. The proper management of parasitic infections addresses several important challenges related to low socioeconomic status and emergent resistance. Therefore, understanding the microbiota's role in interactions with hosts and parasites is crucial for managing parasite diseases with fewer economic and adverse effects associated with pharmaceutical interventions. The current review was divided into three sections. Section 1 focused on the mutual microbiota-host interaction through the purinergic P2X7 receptor (P2X7R) and secretory immunoglobulin A (SIgA). The P2X7R is an abundant intestinal cation channel that is crucial in mucosal immunity, facilitated by SIgA-mediated protection in both innate and adaptive immunity. This study demonstrated that microbiota continually "teach and train" host immunity to attain homeostasis via SIgA production (in T cell-independent and T cell-dependent pathways) and the purinergic receptor P2X7R. In addition, we discussed the potential of manipulating SIgA and P2X7R in immune therapies targeting parasitic infections. Section 2 exhibited parasite-microbiota (microbe-microbe) interactions wherein each can indirectly affect one another through physical and immunogenic alterations and directly via predation, bactericidal protein production, and overlapping of nutrient resources. Thus, microbe-microbe interactions appeared to be multifaceted and species-dependent. Section 3 showed the relationship between microbiota and specific parasites, and the promising role of probiotics. In this section, the review discussed examples of tissue, blood, gastrointestinal, genitourinary, and respiratory parasitic diseases, while highlighting the associated dysbiosis. Furthermore, Section 3 acknowledged the importance of "strain-dependent" biotherapy to boost beneficial microbiota, modulate immunity, and exert anti-parasitic effects.

Keywords: parasites; SIgA; P2X7R; microbiota; dysbiosis; biotherapy

Introduction

The human body hosts a diverse microbiota community consisting of bacteria, fungi, viruses, and protists that coexist in a symbiotic manner [1]. In contrast, parasites are typically dependent on their hosts to flourish and proliferate, often producing harmful toxins while thriving. Parasitic diseases hold significant global importance, causing substantial morbidity and death, particularly in impoverished regions [2]. Additionally, associations between parasitic infections and disrupted microbiota have been highlighted as an important figure of interaction [3]. A healthy microbiota ecosystem contributes to homeostasis, maturation of the immune responses, and regulating innate immunity against microorganisms to counteract pathogen colonization [4,5].

Interactions between the microbiota and parasites can potentially figure out the physical and immunological microenvironment of the host. These interactions can significantly influence the consequences of infections and influ-

ence the host's health status. Parasites can alter the microbiota genera, causing dysbiosis and thus aggrieving host interactions. Conversely, the composition of the microbiota can influence a parasite's capability to colonize itself and reproduce [5].

The World Health Organization has highlighted the growing concern of drug resistance in parasitic diseases, impacting the effectiveness of treatment approaches. For instance, resistance has been observed in various antimalarial drugs, Metronidazole, and Ivermectin [6]. Additionally, chemical drugs proved to trigger dysbiosis and several systemic adverse effects [7]. Recognizing the specific parasite-microbiota and host-microbiota interactions offers innovative therapeutic targets at the molecular level; thus, this understanding can potentially offer effective substitutes for emerging drug resistance.

Probiotics are widely introduced as a biotherapy or bacterio-therapy to substitute chemical compounds. These probiotics exist in multiple forms, including bacteria and yeast, and function by boosting the host's immune system [8,9]. Yet, assessing a definite probiotic strain necessitates a deep recognition of the host-parasite-microbiota interactions at a molecular level.

The current review aimed to represent interactions of microbiota with the host immune factors, secretory immunoglobulin A (SIgA) and purinergic P2X7 receptor (P2X7R), and prospectives in their manipulation as immune therapy (Section 1). Section 2 reviewed the indirect and direct interactions of microbiota with parasitic infection. Finally, Section 3 demonstrated samples for bacterio-therapy in parasitic infections.

Section 1

I: The Interplay between Microbiota and the Adaptive/Innate Host Immunity

Innate Immune Responses

Helminths can affect the body's innate immune reactions to gut microbiota by modulating the expression and sensitivity of specific cell receptors such as toll-like receptors on phagocytes. Moreover, helminths alter the production of antimicrobial peptides (AMPs) in the host, thereby impacting the presence of bacteria, fungi, parasites, and viruses. Microbiota-parasite interactions may also stimulate inflammasome activation which resultantly alters the microbiota, causing dysbiosis. Conversely, the activation of inflammasomes by the microbiota induces a pro-inflammatory environment that effectively eliminates protozoa like *Toxoplasma gondii* [10].

Adaptive Immune Responses

Several genres of gut microbiota such as *Lactobacillus* spp., *Bacteroides fragilis*, *Bifidobacterium infantis*, and *Clostridium* spp., can stimulate T regulatory cells (Tregs), similar to intestinal nematodes [11]. For example, in BALB/c mice, *Lactobacillus taiwanensis* increased Treg cells and thus facilitated the establishment of *H. polygyrus* infection. Additionally, studies with germ-free murine models demonstrate reduced infectivity and/or hatching of whipworms [12,13]. This interaction between parasites and microbiota creates a cooperative environment that fosters tolerance, supporting their persistence and growth. However, any disturbance to either community may disrupt this balance, potentially leading to disease [13]. Yet, in an obese mouse model, excretory-secretory products from hydatid cysts reduced the translocation of mucosal bacteria, amelioration of colon inflammation, upgraded the expression of zonula occludens-1, and repaired gut barrier and mucus production [14].

II: The Mutual Interactions between Microbiota and SIgA and P2X7R in both Innate and Adaptive Immunity (Microbe-Host-Interaction)

The microbiota plays a vital role in stimulating, teaching, and regulating the host's immune system. Consequently, the immune system is developed to maintain symbiosis with its diverse microbial inhabitants. Functioning in optimal rhythm, these host immunity-microbiota interactions promptly protect the host against pathogenic agents and preserve the regulatory mechanisms vital to tolerating harmless antigens. Recently, the focus has turned toward exploring the parasite's microenvironment in the host. Recent literature highlights the significance of immunoglobulin A (IgA) and the activation of the purinergic P2X7 receptor (P2X7R) within the enteric microenvironment, particularly in intestinal mucosal immunity. The collaboration of these molecular structures with the enteric microbiota and their role in preserving homeostasis through innate and adaptive immunity remains an ongoing area of research [15]. Thus, in this section, we aimed to exhibit the mutual relationship of IgA and P2X7R with microbiota during their production as a part of mucosal immunity.

Secretory IgA

SIgA stands out as the primary immunoglobulin present on the mucosal surfaces [16]. Physiologically, IgA production occurs through the T cell-independent (TI) pathway produced in innate immunity and the T cell-dependent (TD) pathway that takes place in the lymphoid follicles (Peyer's patches) of the small intestine [17].

T Cell-Independent (TI)-SIgA Production

The TI pathway operates within innate immunity wherein the produced TI-SIgAs are capable of interacting with a large territory of flora [17]. TI-SIgA is generated by stimulated B cells in the absence of T cells outside of Peyer's patches. Dendritic cells contribute to this process by secreting factors like transforming growth factor-β, B-cell activating factor (BAFF), and A proliferation-inducing Ligand (APRIL), fostering a microenvironment conducive

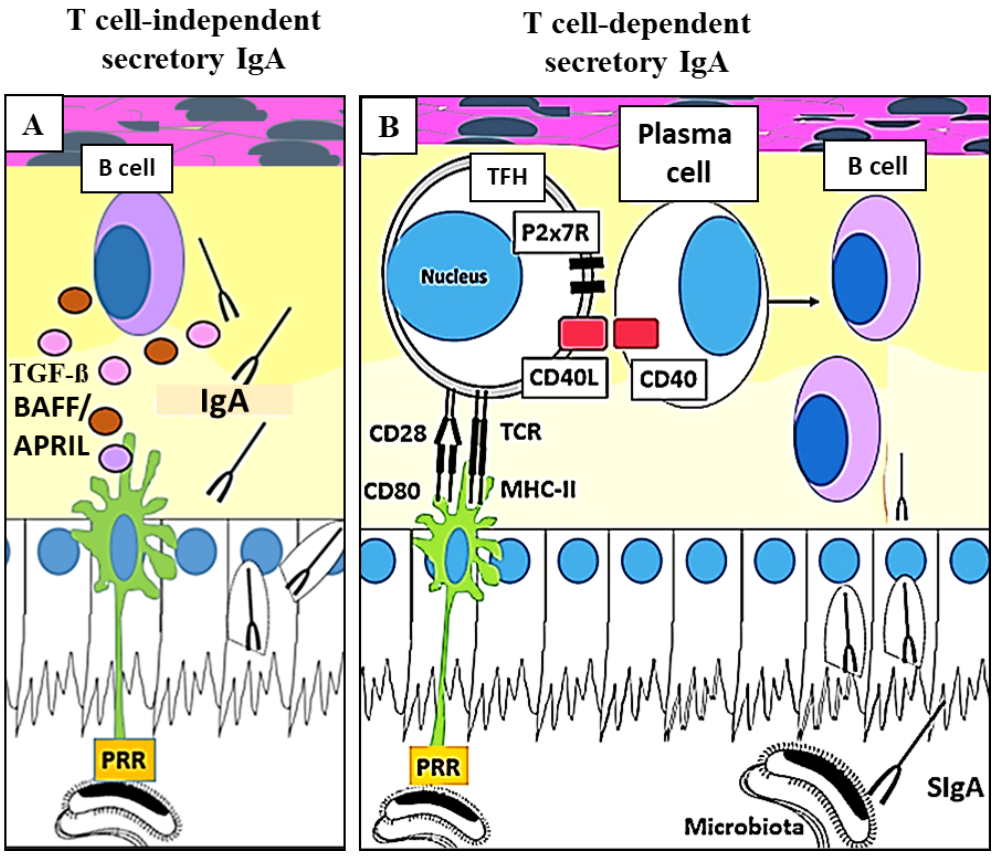

Fig. 1. The possible role of microbiota in figuring out secretory immunoglobulin A (SIgA). (A) In T cell-independent pathways. (B) In T cell-dependent pathways. The figure has been drawn by the authors through the PowerPoint presentation program (version 16, Microsoft, Los Angeles, CA, USA). BAFF, B-cell activating factor; APRIL, A proliferation-inducing Ligand; IgA, immunoglobulin A; CD40, B cells cluster of differentiation 40; TFH, T follicular helper; TGF-β, transforming growth factor-β; PRR, pattern recognition receptors.

to IgA production [18]. In the porcine model, TGF-β (transforming growth factor-β) was found to exert a vital role in the regulation of the differentiation and survival of IgA-secreting B cells by inducing the Bax/Bcl2-Caspase3 apoptotic pathway in Immunoglobulin M (IgM)-secreting B cells [19]. Additionally, BAFF and APRIL trigger the transition from IgM to IgA antibodies. This mechanism typically generates polyreactive SIgA that covers the microbiota with little specificity, therefore exerting little impact on the microbiota composition [18]. Abokor *et al.* [20] demonstrated that a deficiency of APRIL metabolites diminishes T cell-independent IgA class transition; while secretion of IgA through the T cell-dependent pathway remains unaffected (Fig. 1).

T Cell-Dependent (TD)-SIgA Production

The TD pathway operates within adaptive immunity wherein phagocytic cells, namely resident dendritic cells and specialized microfold epithelial cells (M cells), recognize pathogen-associated molecular patterns (PAMPs) on the surface of pathogens. Antigens are then delivered to the T follicular helper (TFH) cells in the Peyer's patches [21]. Thereafter, activated TFH cells (CD40 ligand) become engaged with the B cells cluster of differentiation 40 (CD40), thus inducing the production of TD-SIgAs targeted against invading flora [17] (Fig. 1). IgA generated by this pathway exhibits somatic hypermutation and affinity selection, resulting in increased antigen specificity and affinity. However, it may remain cross-reactive to the conserved targets on a diverse genre of bacteria. TD-SIgAs coat distinct subsets of the microbiota and affect the composition of the microbiota [18]. In addition, the P2X7R plays an important role in controlling TFH cells within the Peyer's patches, thereby enabling TD-SIgAs to shape beneficial microbiota in the host and protect them from enteropathogens [22].

Collectively, SIgA production figures out the colonization and dissemination of microbiota. McLoughlin *et al.* (2016) [23] speculated that SIgA in the mucosa acts as an adhesion-promoting factor that can stabilize biofilm communities. Notably, monoclonal SIgA was found to show cross-species reactivity due to the communal surface structures between bacterial taxa [24,25]. Chen *et al.* (2020) [26] deduced that several clones of affinity-matured and microbiota-reactive SIgA primarily interact with the

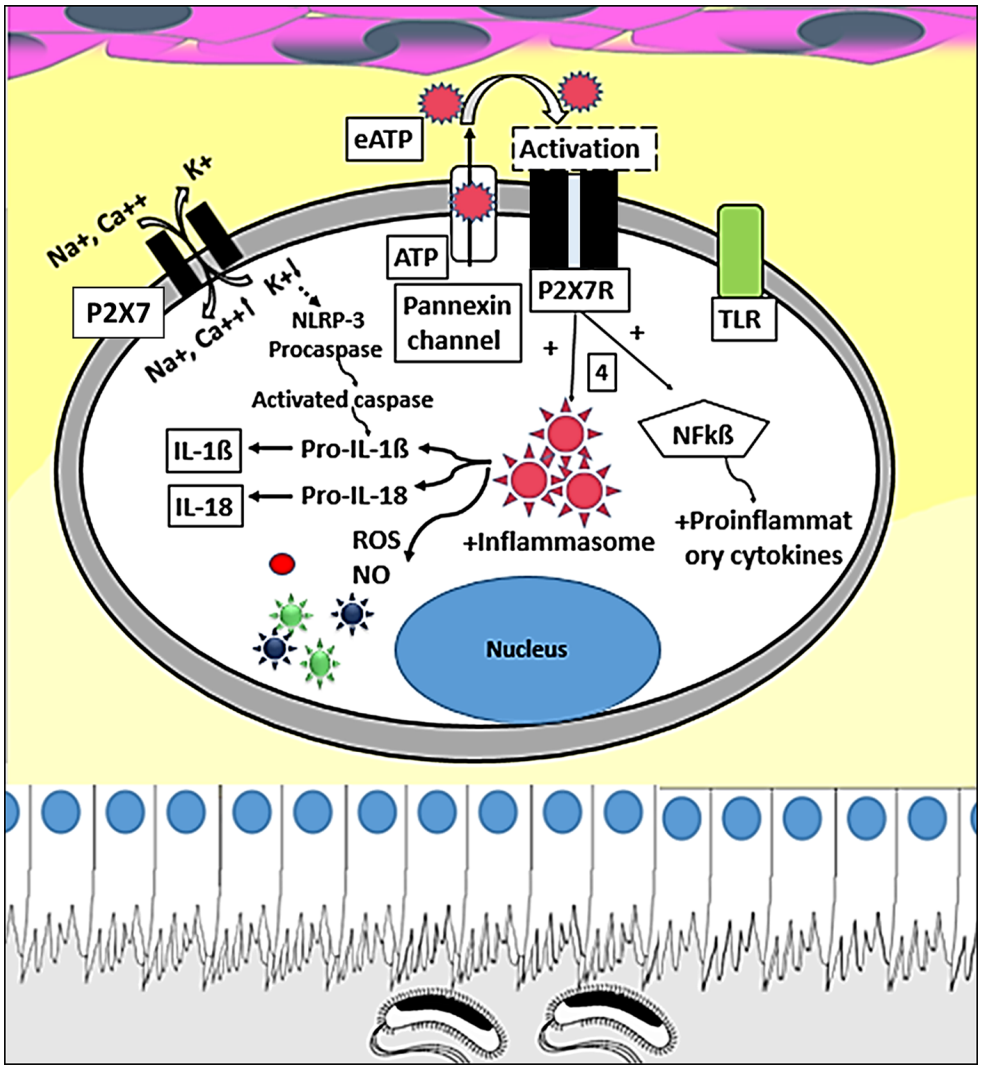

Fig. 2. P2X7 receptor on macrophages. Its activity as a cationic channel when exposed to low concentrations of extracellular adenosine triphosphate (eATP) results in a low-amplitude current in the receptor, i.e., beneficial immunity. The figure has been drawn by the authors through the PowerPoint presentation program. NFKβ, nuclear factor kappa-light-chain-enhancer of activated B cells; ROS, reactive oxygen species; NO, nitric oxide; TLR, toll-like receptor; IL-18, interleukin-18.

microbial glycan structures. Sterlin *et al.* (2020) [25] identified repetitive glycan motifs in bacteria surface structures such as lipopolysaccharides, teichoic acid, and extracellular capsules. Moreover, SIgA undergoes glycosylation, a characteristic that enhances its interaction with these glycans motifs, particularly in the Gram +ve flora [24,25]. Notably, some bacterial commensals possess immunogenic proteins and superantigens capable of stimulating SIgA [27]. Yet, Donaldson *et al.* (2018) [28] determined that SIgA remains a highly strain-specific immunoglobulin even if it is cross-species or glycan-reactive [29]. Accordingly, in the case of invading organisms, the educated immune system responds with activated SIgA, leading to interactions that promote growth and classic agglutination, thereby excluding pathogens from the immune system [30]. In this regard, dysbiosis induces dysfunction of SIgA.

IgA-Microbiota Interaction as Immune Therapy

A study by Hassan *et al.* (2023) [31] implicated the mutual relationship between SIgA and the microbiota in the treatment of intestinal giardiasis by using *Giardia*-infected mice orally provided with supplements containing prebiotics and probiotics. The results demonstrated a substantial reduction in *Giardia* cysts and a notable improvement in the ultrastructure and histology of the intestinal tissue. Furthermore, there was a significant increase in the immunohistochemical and serological IgA levels. Similarly, a recent study highlighted the role of IgA as an immune therapy in viral infections like poliovirus, rotavirus, SARS-CoV-2, and influenza virus [32]. These findings provide a foundation for similar studies in parasitic diseases, particularly in vulnerable immunocompromised patients.

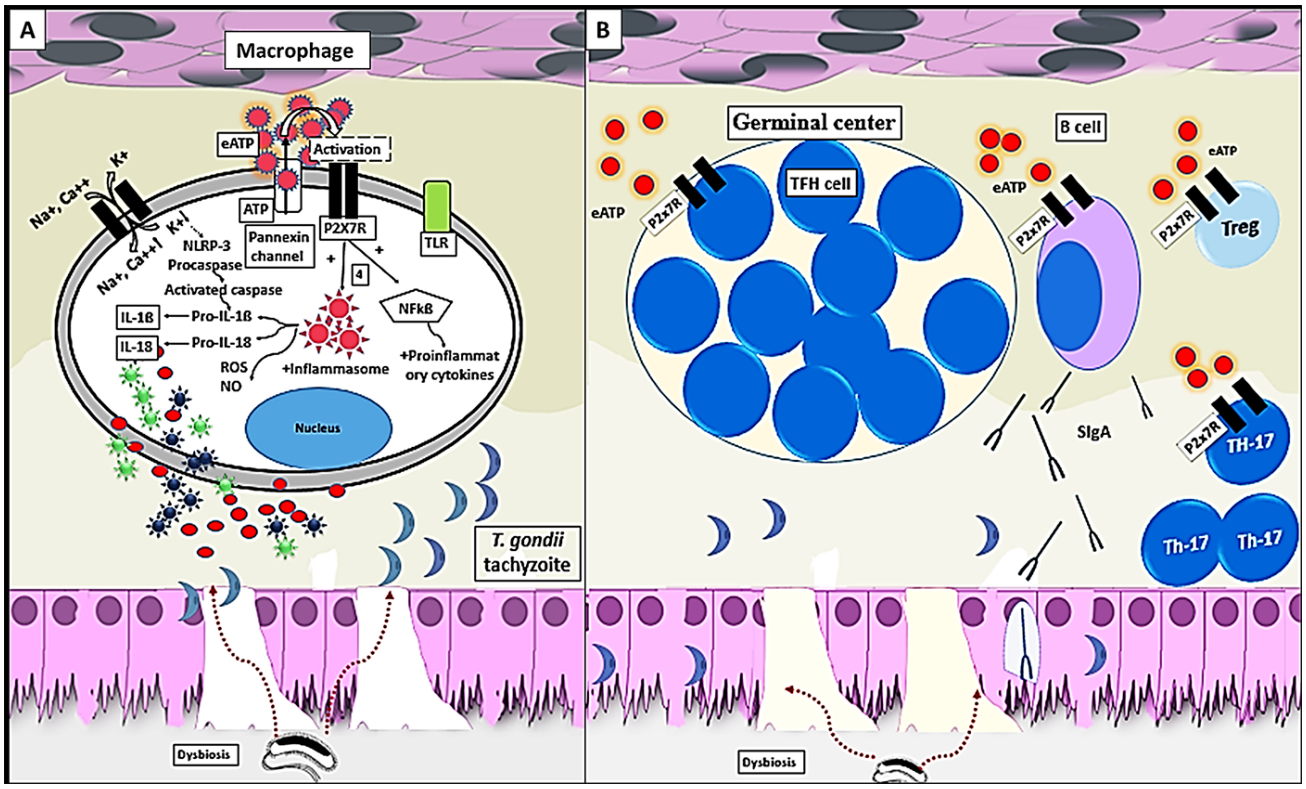

Fig. 3. P2X7 receptor with increased eATP. (A) Activated inflammasome and nuclear factor kappa-light-chain-enhancer of activated B cells (NFKβ), and increased production of ROS, NO, IL-18, and IL-1β. (B) The proliferation of T follicular helper (TFH), the polarization of T helper 17 (Th17), and suppression of T regulatory cells (Tregs), i.e., damaging immunity. The figure has been drawn by the authors through the PowerPoint presentation program.

Using IgA as an antibody-based therapy represents a novel approach to treating specific tumors. A cohort study identified an immunogenic peptide motif within Mycobacterium bovis Bacillus Calmette-Guérin (BCG) heat-shock protein 65 (HSP-65) as a dominant epitope to trigger humoral immunity. Raised serum levels of IgA and IgG anti-HSP-65 titers were related to positive patient outcomes [33]. We inquired if a similar line of treatment combined with boosted SIgA may enhance its therapeutic effect in *Schistosoma haematobium*-associated bladder cancer.

Additionally, intravenous IgA and IgM-enriched immunoglobulin therapy efficiently eradicated pathogens and modified both pro- and anti-inflammatory reactions in sepsis [34]. In this regard, this study investigated if a similar strategy of immune therapy boosted with IgA-triggering functional food might be beneficial in the acute stages of parasitic infections like acute filariasis and the early migratory phase of *Trichinella spiralis* infection.

It is plausible that correspondence between allergic asthma and upper respiratory tract secretory immunity alterations can influence susceptibility to bacterial infection and overall microbial composition [35]. Schwarze *et al.* (1998) [36] suggested the use of SIgA in treating house dust mite (HDM) allergy, demonstrating that allergen-specific IgA in allergen-sensitized murine models modulated the responsiveness of the airway and reduced lung eosinophilia. Takabayashi *et al.* (2003) [37] speculated about the potential efficiency of intranasal IgA immunotherapy to induce tolerance to airway allergens in TH2-sensitized mice. Yet, boosting live intestinal microbiota with probiotics can induce humoral immunity and natural IgA production [38], concurrently establishing mucosal and systemic homeostasis [39]. Of note, IgA production occurs in a strain-specific manner even in the same species of bacteria [40]. In a prior experiment with germ-free mice, IgA was produced against specific strains of Bacteroides thetaiotaomicron, various other Bacteroides species, and unrelated bacterial species like Lactobacillus, Bifidobacteria, and Akkermansia. However, IgA production did not react to certain other bacterial species [40,41]. This study suggested that it is important to specify species and bacteria strains used as probiotics in clinical and experimental HDM allergy studies to promote positive outcomes.

P2X7 Receptor

The P2X7R is an ionotropic purinergic receptor that is activated by the extracellular adenosine triphosphate (eATP), functioning as an ATP-gated channel. P2X7R exhibits selective expression on the surface of the dendritic cells, macrophages (M2), and other immune cells.

i. P2X7R in Innate Immunity

Physiologically, at low eATP levels, the P2X7R stimulates the production of interleukins (ILs), reactive oxygen species (ROS), and nitric oxide (NO); however, these unstable molecules may cause cellular damage. Additionally, these receptors trigger inflammasomes, leading to the release of IL-1β (Fig. 2). In instances of pathological cells, eATP levels increase, activating the P2X7R in the immune cells. Consequently, the P2X7R induces further release of eATP molecules via pannexin hemichannels that react proactively to environmental stresses, thus, intensifying inflammatory reactions.

ii. P2X7R in Adaptive Immunity

The functional P2X7R on lymphocytes activates effector T cells, stimulates the expansion of TFH cells in the Peyer's patches (germinal centers), stimulates the production of SIgA by B cells, polarizes T helper 17 (Th17) cells, and suppresses the viability and functionality of T regulatory cells (Tregs) [42,43]. However, in an inflammatory microenvironment with increased eATP levels, sustained P2X7R activation leads to the opening of catalytic pores, resulting in cell apoptosis and necrosis, perpetuating a self-sustained pro-inflammatory lethal cycle [44]. A therapeutic trial utilizing a purified enzyme, nucleoside diphosphate kinase, demonstrated inhibition of P2X7R, plasma membrane permeabilization, and the prevention of cellular apoptosis by hydrolyzing ATP [45].

Dysbiosis and altered microbiota, coupled with activated P2X7R, induce inflammasomes and amplify inflammatory responses [46] (Fig. 3). In this context, the administration of probiotics to restore and strengthen the altered intestinal microbiota in anti-parasitic therapeutic trials holds promise, as will be further discussed in Section 3. Yet, the capability of probiotic treatment to counteract the deleterious activation of P2X7R/inflammasome in parasitic diseases remains inadequately studied.

Targeting P2X7R as Immune Therapy

Therapies aimed at blocking P2X7R have gained popularity for several diseases, ranging from inflammatory disorders to cancer. Successful therapy should mitigate activated P2X7R without disrupting its physiological role as it primarily controls the numbers of the TFH in Peyer's patches. However, according to Proietti *et al*. (2014) [47], blocking the P2X7 axis in TFH cells could trigger reactions in the germinal center, resulting in increased secretion of high-affinity SIgA that interacts with the flora. Consequently, this may lead to a reduction in mucosal bacteria and hinder the systemic translocation of bacterial components, subsequently diminishing the stimulation of B1 cells and IgM serum levels. In murine models, the lack of P2X7 was therefore related to higher vulnerability to polymicrobial sepsis.

Regarding the aforementioned insights, the introduction of P2X7R-blocking therapies in parasitic diseases warrants careful investigation. For instance, in bladder cancer, P2X7R has been identified as a key mediator of inflammation and cancer progression, particularly in terms of invasiveness and metastasis. Thus, P2X7R antagonists were regarded as potential anti-metastatic therapeutic agents [48]. However, in *Schistosoma*-associated bladder cancer, there's a shift in the microbiome, mainly dominated by Firmicutes and Proteobacteria, altering the microbiota structure. Besides, several immune stimulatory bacteria such as *Enterococcus* spp. *Fusobacterium* spp. and *Sphingobacterium* spp. are linked to urinary schistosomiasis-triggered bladder pathologies [49]. Therefore, we propose that the biological activity of the P2X7R antagonists in *Schistosoma*-associated bladder cancer (as an example) should be assessed to guard against the simultaneous spread of sepsis.

Another model is HDM-triggered allergy wherein the stimulation of the eATP/P2X7R axis triggers the nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome assembly, leading to pro-caspase 1 cleavage into active caspase 1. This process stimulates the extracellular production of IL-1β and IL-18, promoting Th2 cell differentiation [35]. Furthermore, mast cell degranulation is triggered by the stimulation of the eATP/P2X7R axis [50]. A prior study suggested that targeting P2X7R on dendritic cells and eosinophils might be a promising immune therapy for asthma [51]. However, the remote regulation of mucosal immunity in the respiratory tract via oral probiotics remains a subject of debate. According to Antushevich (2020) [52], probiotics do not affect the activity of the inflammasome in healthy individuals; however, rectifying dysbiosis with probiotics alleviates the inflammasome triggering.

Section 2: Parasites-Microbiota (*Microbe-Microbe*) Interactions

This section exhibits microbe-microbe interactions that dramatically alter the gut ecosystem, affecting the overall landscape of parasitic diseases. The microbiota can effectively hinder parasite colonization in the gut, disrupting their replication and virulence. Consequently, this contributes to clinical presentation variability from asymptomatic infection to chronic parasitic disease [53]. Conversely, parasitic infections can alter the host's interaction with its microbiota, either driving or protecting against dysbiosis. In dysbiosis, overgrowth of less beneficial microbes occurs at the expense of physiologically beneficial bacteria, exacerbating the pathology caused by the parasite and disrupting symbiosis [54]. The following item represents the parasite-microbiota interactions as indirect (physical and immunogenic) and direct (predation theory, bactericidal protein production, and overlapping of nutrient resources) effects (Fig. 4).

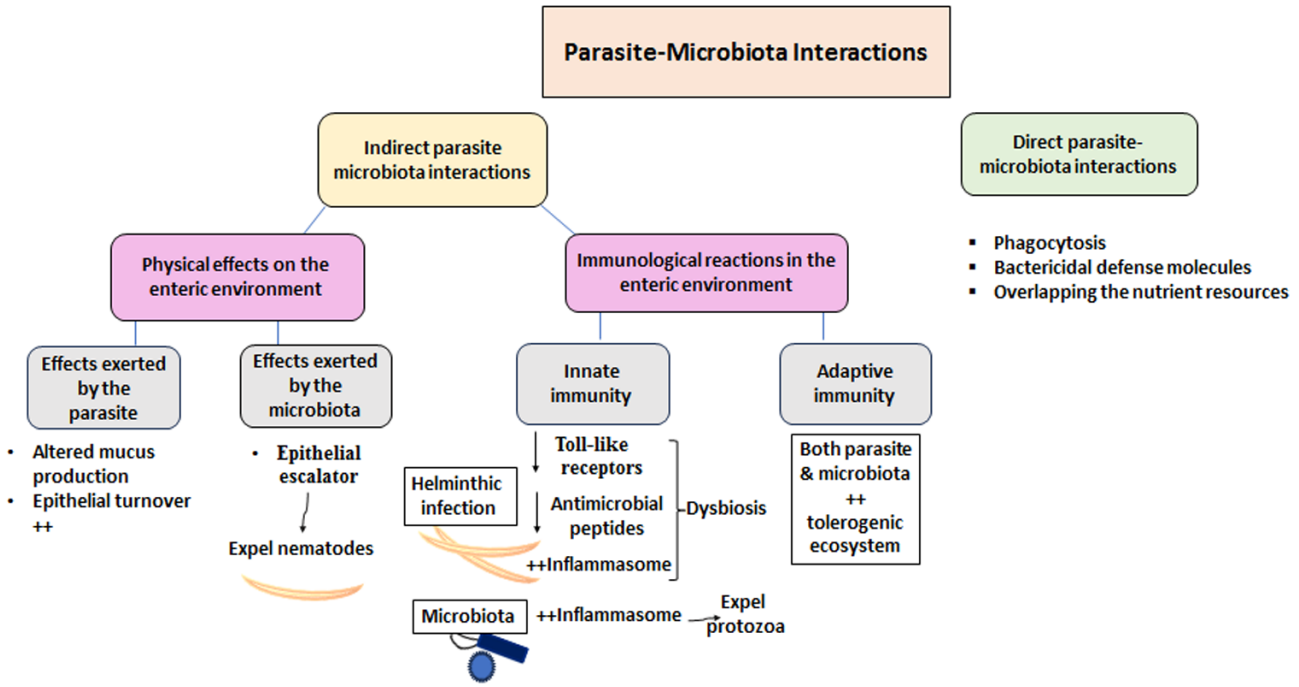

Fig. 4. Parasite-microbiota interactions. The figure has been drawn by the authors through the PowerPoint presentation program.

Indirect Parasite-Microbiota Interactions

This section focused on the indirect impact of parasites and microbiota on one another by altering the physical and immunogenic milieu of the enteric microenvironment.

i. Microbe-Microbe Physical Interactions

Parasite-triggered physical interactions. Gut colonization by parasites affects the inhabitant microbiota by re-engineering the physical structure of the mucosal barrier by the following mechanisms.

Parasites can alter the chemical composition and production of mucus, impacting the microbiota's balance positively or negatively. The inhibitory effects of parasites on microbiota may be exerted by altering its attachment to the epithelial surface, changing its accessibility to nutrients, in addition to causing disorders in its evacuation out of the gut [53]. However, the parasite-induced increase in mucus production might upgrade the abundance of some species of microbiota. For instance, species like *Verrucomicrobia*, *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* consume carbohydrates from mucus as a source of carbon and the mucus-utilizing genus like *Clostridiales* increases with the abundance of mucin composition [55].

Gut parasites like helminths accelerate the turnover of the epithelial monolayer causing potentially debilitating effects on the gut-dwelling microbes. Selectively, microbiota with high replicating rates may evade evacuation from the gut. Additionally, protozoan pathogenesis may evolve parasite attachment, the distraction of tight junctions, cell invasion, or epithelial cell damage. Interactions between intestinal host mucins and the four major protozoa to attain colonization and establishment have been deduced by Martínez-Ocaña *et al.* (2020) [56]. In *Giardia intestinalis* infection, the parasite secrets lectin-like structures that chiefly comprise complex oligosaccharides, N-acetylglucosamine, mannose, and sialic acid that interact with the host mannose-binding lectins. *Cryptosporidium* spp. and *E. histolytica* produce the lectin galactose/N-acetyl-D-galactosamine (Gal/GalNAc), which enables their adhesion to the epithelial cells. Also, *E. histolytica* the Gal/GalNAc lectin possesses both hemolytic and cytotoxic actions. *Cryptosporidium* spp. adheres and form an adhesion-attack complex through glycoproteins (gp-30, gp-40/15, and gp-900) and the glycoprotein lectin. *E. histolytica* and *G. intestinalis* secret glycosidases e.g., α-d-glucosidase, β-N-acetyl-D-glucosaminidase, β-mannosidase, and β-d-galactosidase. *Blastocystis* spp. produces on its surface chitin, sialic acid, α-D-glucose, α-D-mannose, α-D-fucose, Glc-NAc, and Fucosidases that are supposed to play a role in the degradation of mucin. Therefore, gut microbes come in great contact with the epithelial barrier or even translocate across it, as observed in infections like amoebiasis, cryptosporidiosis, and giardiasis [56].

Microbiota-Triggered Physical Interactions

The microbiota's influence extends to mucin biosynthesis at the molecular level, directly affecting the colonization, persistence, and fertility of several parasites. Additionally, gut microbiota alters the turnover of the intestinal epithelial cells (IEC). For example, Gram +ve bacteria mediate gastrointestinal tract repair and increase IEC turnover, specifically, the epithelial escalator, which helps expel ne-

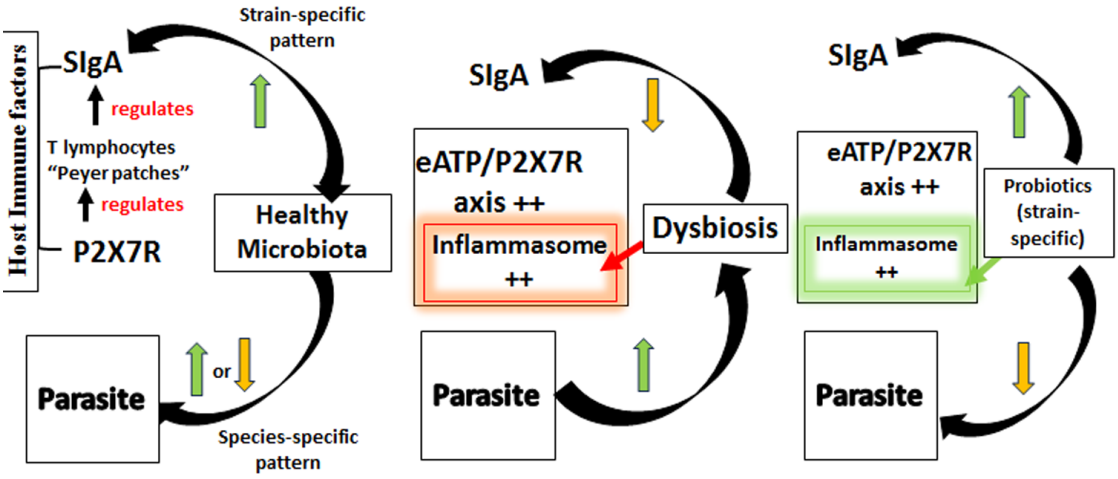

Fig. 5. Parasite immunogenic interaction. The figure has been drawn by the authors through the PowerPoint presentation program.

matodes and hinder their colonization [57]. Yet, another model showed that *Escherichia coli* triggers the hatching of *Trichuris muris* eggs [58].

ii. Microbe-Microbe Immunogenic Interactions

Both parasites and microbiota can affect one another indirectly by altering the gut's immune context. However, this did not appear to act in a single-track model (Fig. 5).

Direct Parasite-Microbiota Interactions

These interactions primarily rely on the extended coexistence of parasites and gut microbiota. Several parasite genera depend on the microbial composition inside their host to successfully exploit parasitism. For instance, germ-free animals were found to resist colonization with some helminthic infections, including *Heligmosomoides polygyrus*, *Trichinella spiralis*, and *Nippostrongylus brasiliensis* [53]. These micro-microbe interactions appeared to occur via the following mechanisms:

Theory of Phagocytosis "Predation"

The relationship between eukaryotic parasites and prokaryotic microbiota resembles a predator-prey dynamic, where helminths or protozoa utilize enteric bacteria as a nutrient source [53]. For instance, in children, *Dientamoeba fragilis* is associated with increases in 16 genera of microbiota, notably *Victivallis* and *Oscillibacter*. Moreover, metronidazole treatment led to changes in microbial composition, with bacteria like *Hungatella* spp., *Veillonella* spp., *Ruminococcus* spp., *Flavonifractor* spp., *Sutterella* spp., and *Streptococcus* spp. showing increased growth and *Eubacterium* spp. and *Coprococcus* spp. exhibiting reductions [59]. Bacterial DNA found in *D. fragilis* extracts implicated Gram -ve bacteria as a crucial nutrition [60]. This interrupted microbiota composition may explain the corresponding gastroenteritis present in patients solely infected with *D. fragilis* without other parasites [61].

Entamoeba, like other protozoa, relies on the phagocytosis of bacteria as a source of nutrition. Therefore, the colonization of *E. histolytica* and its associated symptomatology is dependent on the composition of the microbiota, particularly the *Prevotellaceae* family. Researchers used species-specific assays, *E. histolytica* II enzyme-linked immunosorbent assay (ELISA), an in-house ELISA for anti-*E. histolytica* lectin immunoglobulin A (IgA), anti-galactose/N-acetyl-D-galactosamine (anti-Gal/GalNAc), and a species-specific quantitative polymerase chain reaction (qPCR) assay on DNA extracted from feces of 392 children with enteric infections [62].

E. histolytica phagocytoses enteropathogenic bacteria like *Escherichia coli* and *Shigella dysenteriae*, which prompt virulence and invasion of *Entamoeba* in the host epithelium, causing dysentery [63]. Verma *et al.* (2012) [64] reported substantial increases in *Bifidobacterium*, while *Bacteroides* spp., *Lactobacillus* spp., *Clostridium leptum*, *Clostridium coccoides* subgroup, *Campylobacter* spp., and *Eubacterium* spp. become reduced. Interestingly, the virulence of amoeba seems reliant on its interaction with the intestinal microbiota. *E. histolytica* can convert microbiota into a pathogenic profile as it favors the phagocytosis of healthy bacteria such as *Lactobacilli* [65]. In a prior metagenomic analysis based on rRNA, *E. histolytica* was found to favorably phagocytose several species of beneficial bacteria such as *Erysipelotrichales, Bifidobacteriales, Lactobacillales,* and *Clostridales,* thus affecting gut homeostasis [66]. Phagocytosis of pathogenic *Escherichia coli* by *Entamoeba* aggravated the associated damage of the mucosal epithelium. The *Enterobacteriaceae* can render *E. histolytica* more resistant to oxidative stress, thus allowing colonization of the enteric mucosa [66–68]. Conversely, *Giardia duodenalis* and *Blastocystis hominis* can trigger significant alterations in the gut microbiome.

Table 1. The relationship between the parasitic immune reaction and probiotics.

Parasite	Immune reaction	Dysbiosis-parasite interaction	Determined probiotics	Reference
Toxoplasma Gondii	P2X7 & Inflammasome	Increased: Bacteroidaceae, Rikenellaceae, Rhodospirillales *Clostridia* Reduced: Muribaculaceae Lactobacillaceae • Progression from acute to chronic toxoplasmosis. • Cachexia in chronic disease.	Koumiss treatment Lactobacillus acidophilus	[79–86]
Plasmodium	P2X7~Th1 versus TFH, Th2, & Ab production (*fine tune*)	Alteration in filamentous gut microbiota affects TFH cells, plasmablasts, & B cells in the germinal center	*Lactobacillus casei*	[87–95]
Giardia lamblia	Inflammasome, pro-IL-1β & pro-caspase-1	The composition of the microbiota affects Th17, Tregs, and the severity of giardiasis.	*Saccharomyces*, *Lactobacillus rhamnosus GG*, *Lactobacillus johnsonii La1*, *Lactobacillus gasseri* CNCM-I 4884, Weissella paramesenteroides-WpK4, Bifidobacterium longum-51A	[96–107]
Trichomonas vaginalis	• P2X7 & inflammasome • Pyroptosis	• *Lactobacilli decreases* • Triggers inflammation	*L. jensenii*, *L. crispatus*, *L. mucosae*, *L. vaginalis*, and *L. acidophilus*	[108–114]
House dust mite	eATP/purinergic receptor (P2Y2), apoptosis & cytokine production	• NK T cells trigger Th2 differentiation • Secretion of Ig E, IL-4, & IL-13 increases • Lysis of IgA and stimulation of basophils & mast cells • Aggravation of asthma	*Lactobacilli, living and dead Faecalibacterium prausnitzii*	[115–121]
Entamoeba histolytica	• Modification of goblet cell differentiation and reduction of mucus assembly in germ-free murine models • Modification of tight junction proteins • Distortion of epithelial barrier permeability • Two amoebic regulatory patterns were documented with enteric bacteria but not with probiotics: - Altered expression of the LRR family genes. - Gene Regulation.	Phagocytosis of a few beneficial bacterial species involving *Lactobacillus ruminus* Increased *Bifidobacterium* species in faecal samples especially *P. copri* Protection of *E. histolytica* against oxidative stress Translocation of intestinal microbiota into mucosal surfaces as well as spreading to other organs	Probiotics (Bacteroides, Clostridia, Campylobacter, Lactobacillus, and Eubacterium): Elevation of colon levels of interleukin 17A, dendritic cells, and neutrophils. Anti-proliferative influence on Entamoeba via regulation of amoebic genome.	[122–127]

LRR, Leucine-rich repeat; CNCM, the National Collection of Cultures of Microorganisms.

Interestingly, the bacterial species are not equally liable to predation by protozoa. Additionally, bacteria may defend against predation via multiple mechanisms and may render symbiotic or parasitic forms. To resist predation, bacteria form biofilms with distinct structures and biochemical compositions, often resulting in reciprocal effects on the protozoa's virulence [69].

Bactericidal Protein Production

Several helminths can produce helminth defense molecules which are peptides similar to human antimicrobial peptides. Helminth defense molecules exhibit both direct bactericidal properties and immunomodulatory effects by modifying host immune reactions. Resultantly, this enhances their colonization and parasitism inside the host [70]. Additionally, gastrointestinal helminths are suggested to produce excretory-secretory products (ESPs) with antimicrobial characteristics that can actively alter microbiota [56]. Several authors determined that these ESPs comprise antimicrobial peptides and proteins like lectins and cystatin produced by *A. suum* [53,56,71]. Likewise, ESPs produced by *H. polygyrus* have antimicrobial properties against various bacteria like *Escherichia coli, Enterococcus faecium*, and *S. aureus* [72]. The helminth-secreted extracellular vesicles also influence worm-microbiota interactions, leading to rearrangements in the microbial communities [73].

Overlapping of Nutrient Resources

Finally, direct interactions between parasites and microbiota can involve competition for nutrients or cross-feeding, where one species utilizes the byproducts of another. Hadadi *et al*. (2021) [74] highlighted the significant role of the enteric microbiota in the *de novo* biosynthesis of numerous micronutrients, maintaining the balance of vitamins and minerals. For instance, *Escherichia coli* is vital for the bioavailability of iron, folic acid, and vitamin B12 [75]. Conversely, parasites like *Diphyllobothrium latum* are known to consume vitamin B12 [76], and a recent study in rural Tanzania linked anemia and micronutrient deficiencies in children to the burden of parasitic infections [77].

In this regard, parasite-microbiota interactions appeared to be species-dependent. A key feature of these interactions is an organism's ability to create an environment favoring its growth while impeding the survival of other organisms. Therefore, each parasite appeared to have unique biological and metabolic properties and the introduction of therapeutic microbes is assumed to differ from one parasite to another.

Section 3: The Relationship between Microbiota and Specific Parasites and the Promising Role of Probiotics

Various microenvironmental factors influence the direction of host-parasite-microbiota interactions. Previous probiotic trials have shown efficacy in boosting natural immunity in parasitic diseases, modulating the enteric microenvironment, and competing for occupation as a primary biotype. The principal goal of this process is to hinder parasites and reduce clinical symptoms. Both human clinical studies and experiments on laboratory-bred animals supported probiotics as adjunct therapies [78] (Table 1, Ref. [79–127]). However, debates persist regarding the safety of probiotics and their potential risks when administered [128–130]. This could be attributed to the multifaceted microbe-microbe interfaces (demonstrated in Section 2) or a deficit in host immune factors such as SIgA and P2X7R. Despite these debates, this section aims to review successful examples of probiotics within the inflammatory microenvironment associated with various parasite species.

Toxoplasma gondii

Transmission of *T. gondii* occurs through several routes involving the consumption of food and water contaminated with sporulated oocysts. Dysbiosis intensifies during acute toxoplasmosis, whereas the diversity and abundance of beneficial flora decrease at the chronic stage of infection, independent of the parasite genotype [79]. In 2023, Moreira-Souza *et al*. [80] highlighted the vital role of P2X7 in *T. gondii* infection in mice. They observed that P2X7 triggered the inflammasome, enhanced protective immunity, and regulated local and systemic immunity. Suppression of pro-inflammatory cytokines (IL-12, IL-1β, interferon-gamma (IFNγ), and Tumor necrosis factor alpha (TNFα)) in P2X7-/- murine models increased vulnerability to *T. gondii* and tissue destruction. The severity of the disease was defined by specific microbiota populations regulated by P2X7 [80]. In this context, Miller *et al*. [81] determined that the lack of P2X7 increases vulnerability to toxoplasmic ileitis. Experimentally, both wild-type (WT) and P2X7-/- mice infected with *T. gondii* showed increases in the bacteria species of Bacteroidaceae, Rikenellaceae, and Rhodospirillales while reducing the growth of Muribaculaceae and Lactobacillaceae. P2X7-/- mice had increased growth of Bacteroidia and Tannerellaceae. Yet, P2X7-/- mice lacked the growth of Clostridiales and Mollicutes bacteria that expanded in WT mice [81]. Shao *et al*. (2020) [82] deduced that changes in gut microbiota exert a vital role in the progression of the disease from acute to chronic infection. Furthermore, Hatter *et al*. (2018) [83] associated chronicity in toxoplasmosis with cachexia and dysbiosis.

An investigation into koumiss treatment's effect (fermented mare's milk) on *T. gondii*-infected mice revealed increases in *Lachnospiraceae* and *Akkermansia muciniphila*

in the intestinal flora via specific metabolic pathways. Thus, koumiss treatment appeared to rectify dysbiotic changes caused by the parasitic infection. Interestingly, koumiss notably decreased parasite cyst counts in the brains of infected mice and countered *T. gondii* reactivation in immunocompromised murine models [84]. These benefits might be attributed to koumiss' indirect support to the intestinal microbiome due to its rich composition of vitamin C, calcium, phosphorus, pantothenic acid, vitamins A, E, B2, and B12, and essential fatty acids like linoleic and linolenic acid. Additionally, koumiss is rich in lactose that is fermented by bacteria into lactic acid [85]. Probiotics in toxoplasmosis challenged with diabetes reduced the cerebral parasite load, enhanced intestinal claudin-1 and amended the expression of IL-17A and programmed cell death protein-1 (PD-1) in the enteric and cerebral cells [86].

Plasmodium (Plasmodiidae)

Transmission occurs through infected female Anopheles mosquitoes, depositing sporozoites into humans during a blood meal. ATP levels rise in infected red blood cells (RBCs) in *Plasmodium* infection, either released extracellularly via ion channels or due to RBC rupture. These eATP molecules activate the P2X7 receptor, promoting Th1 cell differentiation during the blood stage of the parasite. Nevertheless, murine models peritoneally infected with *Plasmodium chabaudi* showed P2X7 promoting apoptotic-like cell death in TFH cells in the spleens, fine-tuning Th1 and TFH cell differentiation [87]. The circulating TFH cells and Th2 contribute to anti-*Plasmodium*-antibody production [88], influenced by the gut microbiota's impact on CD4 T-helper cells [89]. The filamentous commensal bacteria can influence TFH cell differentiation and their translocation from Peyer's patches (germinal centers) in the intestine to systemic lymphoid areas [90]. The gut microbiota can influence malaria resistance by activating TFH and inducing proper humoral responses [91]. In turn, changes in gut microbiota during malaria affect TFH cells, plasmablasts, and B cells in the germinal center (GC). Interestingly, Waide *et al.* (2020) [92] showed that low *Plasmodium* burden in murine models was intimately related to gut microbiota that appeared to affect the biology of the splenic GC and the repertoire of the anti-parasite-antibodies. Probiotics have shown an impact on immune resistance to malaria; *Lactobacillus casei* combined with chloroquine inhibited hemosiderosis and parasitemia rate [93,94]. Darwesh and El-Sayed (2022) [95] considered probiotics as a preventive tool for malaria infection, suggesting the potential for novel vaccination strategies. Yet, more studies that specify strains of microbiota and define therapeutic or prophylactic doses are still required.

Diphyllobothrium latum

Transmission of *D. latum*, known as the fish tapeworm, occurs via the consumption of undercooked fish. *D. latum* competes with the host for dietary cobalamin (vitamin B12) or interferes with the host's vitamin absorption by secreting a substance that separates the intrinsic factor from the vitamin in the small intestine. Heavy parasite burdens can lead to megaloblastic anemia, subacute spinal cord degeneration, and cognitive decline. To our knowledge, the role of P2X7R during *D. latum* infection has not been researched. Thus, we propose studies on the P2X7 pathway as an immune target in complicated cases of *D. latum* infections, particularly in neurological cases, to speed up the expulsion of the parasite. Helminthic infections dynamically change the structure of the intestinal microbiota which may also intensify the underlying intestinal pathology [131]. Physiologically, microbiota appears to epigenetically modulate epithelial cells, reducing the expression of C-type lectin involved in cell adhesion, pathogen immune responses, and apoptosis. This modulation hinders pathogen adherence as a part of innate immunity [132]. Microbiota also consumes energy sources needed for pathogen growth [133], produces anti-bacterial compounds, and exerts immunomodulation [134]. Yet, probiotics act as vitamin suppliers for the host, potentially compensating for the absence of certain compounds and enhancing treatment [135]. Notably, microbe-microbe interactions (*D. latum*-microbiota) and the capability of intestinal flora to prevent *D. latum* attachment to the intestinal mucosa remain as research points.

Giardia lamblia

Transmission of *G. lamblia* occurs via the consumption of food and water contaminated with the parasite's cyst stage. Pathogen-associated molecular patterns (PAMP) in *G. lamblia* stimulate inflammasomes, pro-IL-1β, and procaspase-1 as they secrete proinflammatory mediators that protect the host [96]. However, the severity of *Giardia* infections varies with the microbiota composition, regulated by Tregs stimulation and Th17 inhibition [97]. In the same line, dysbiosis is implicated with an immature immune system, impaired growth of Peyer's patches, reduced $CD4^+$ T cells, and lower IgA levels [98]. Moreover, dysbiosis also reduces the density of the villus capillary network [99] and the deconjugation of the bile acid [100]. *Giardia* sheds extracellular vesicles (EVs) that contain virulence factors like miRNA which bind target mRNA to prevent protein production. EVs induce bacterial motility to adhere to the intestinal epithelium and exhibit bacteriostatic effects, reducing the microbiota's ability to synthesize biofilms [101].

Probiotics alleviate gastrointestinal symptoms and the burden of *Giardia* parasites [102]. For example, strains like *Lactobacillus* and *Saccharomyces* increase antioxidant capacity, modify mucosal and systemic immunity, and damage *Giardia* morphology [103]. Oral feeding of *Lactobacillus rhamnosus GG* (LGG) probiotics extracted from *Lactobacillus rhamnosus* increased levels of antioxidants, SIgA, and CD4 T cells but reduced levels of CD8 T cells and INF-

γ [104]. Administration of Weissella paramesenteroides-WpK4 and Bifidobacterium longum-51A in *Giardia*- infected rodents restored mucus secretion and intestinal histology and simultaneously decreased the parasite load [105]. *Lactobacillus johnsonii La1* and *Lactobacillus gasseri* the National Collection of Cultures of Microorganisms (CNCM)-I 4884 contain Bile-Salt-Hydrolase-like activities that are toxic to *Giardia* [106]. Importantly, breastfeeding enhances enteric microbiota due to its rich composition of maternal immunoglobulins, oligosaccharides, bile salts, lysozymes, lactoferrin, and fat globules [107].

Trichomonas vaginalis

Transmission of *T. vaginalis* occurs via sexual contact and predominantly exists extracellularly in the genital organs. To initiate infection, it must attach to the vaginal mucosa. *T. vaginalis* damages host tissue by killing host cells, disrupting microbiota, and triggering inflammation. Metagenomics studies indicate that competition between *T. vaginalis* and *lactobacilli* for the human vagina microecology [108]. *T. vaginalis* triggers increases in eATP and potassium efflux, activating P2X7 and inflammasome in macrophages, leading to the production of IL-1β. Macrophage inflammatory cell death occurs through pyroptosis, facilitated by gasdermin-D protein, which forms pores in the host cell membrane [109].

Combining probiotics with metronidazole decreased inflammation in the vagina, notably reducing pH levels and increasing redox potential by the 4th day of treatment, showing potential effectiveness against Bacterial vaginosis [110]. There is potential to develop vaginal probiotics via clinical *Lactobacillus* isolates. Probiotics derived from isolates belonging to *L. jensenii*, *L. crispatus*, *L. mucosae*, *L. vaginalis*, and *L. acidophilus* are mostly considered. However, some isolates showed significant cytokine production [111].

The cell surface aggregation-promoting factor in *Lactobacillus gasseri* ATCC-9857 inhibits the cytoadhesion of *T. vaginalis* to vaginal ectocervix cells [112]. *L. gasseri* (strain ATCC 9857 and KS 120.1) supplementation can ameliorate the cytotoxic damage exerted by the parasite by delaying cell detachment and disruption in the F-actin cytoskeleton, serving as a physical barrier and exhibiting a pharmacological effect. Additionally, *L. gasseri* KS 120.1 can also produce parasiticidal substances that act on the parasite in a time-dependent manner [113]. Bifidobacterium animalis lactis-BL050, *Lacticaseibacillus rhamnosus*-LRH020, and *Lactiplantibacillus plantarum*-PBS067, either individually or combined, were observed to effectively aggregate with the parasite [114].

House Dust Mite (HDM)

This arthropod induces allergic asthma characterized by eosinophilic airway inflammation and hyper-reactivity. Microbiota is responsible for the maturity of immune function, thus reducing allergic sensitization [115]. Recently, research has targeted the bidirectional cross-talk between intestinal microbiota and the lungs. In cases of dysbiosis, natural killer T cells can trigger Th2 cell differentiation and the production of Ig E, IL-4, and IL-13. So far, lysis of IgA stimulates basophils and mast cells thus aggravating asthma [116]. *Dermatophagoides pteronyssinus* (HDM) disrupts the metabolism of aromatic acids that are essential for maintaining normal biological functions [117]. HDM induces the release of IL-33, which regulates immune responses in barrier tissues like the skin. This release occurs following activation of the eATP/purigenic receptor (P2Y2), known for its involvement in apoptosis and cytokine secretion [118].

Resident microbiota can trigger the Th1 cytokine profile, IgA, IL-17, and Tregs [119]. *Lactobacilli* impact Tregs by enhancing the production of semi-mature dendritic cells and the expression of CD-40 molecules. In addition, it enhances the production of the regulatory cytokines, TGF-β and IL-10 whereas IL-4 and IL-5 are inhibited [120].

A new line of probiotics containing live *Faecalibacterium prausnitzii* was found to enhance *Streptococcus*, *Faecalibaculum*, and *Dubosiella*. Even killed *F. prausnitzii* improved the growth of *Muribaculaceae* and *Parabacteroides*. Both living and dead *F. prausnitzii* increased *Lachnoclostridium* growth. *F. prausnitzii* was found to normalize the metabolic pathways related to short-chain fatty acids and reduce the production of IL-4, IL-5, IL-13, and IgG1 while increasing Tregs and improving dysbiosis. Therefore, *F. prausnitzii* yields an anti-asthmatic effect and can be proposed for the prevention of allergic asthma [120]. Notably, Early-life antibiotic treatments were observed to moderate Tregs, potentially reducing the severity of allergic asthma induced by HDM in mice [121].

Entamoeba histolytica

Transmission of *E. histolytica* is feco-oral and occurs via the cyst stage of the parasite. *Entamoeba histolytica* is the only species of amoeba considered virulent and harmful to the host causing dysentery [122]. Using its virulence factors, the parasite interacts with native bacteria, distracts the mucus layer, and adheres to the epithelium. The toll-like receptor 4 (TLR4)-binding domain of peroxiredoxin in the parasite stimulates NLRP3- Inflammasome in macrophages, increasing the secretion of IL-1β/IL-18 [123]. Complications of *E. histolytica* infection include liver abscesses, acute fulminant necrotizing colitis, and multifocal perforations in the colon [122]. Thus, P2X7 may be a potential immune target for fulminant cases. Yet, Yanagawa *et al.* (2019) [124]. deduced that dysbiosis affects the clinical presentation of *E. histolytica* infection, favoring symptomatic colitis to the asymptomatic chronic forms. *E. histolytica* selectively phagocytoses beneficial bacteria, particularly those from *Lactobacillales* (*Lactobacillus ruminus*), *Erysipelotrichales*, *Bifidobacteriales*, and *Clostri-*

dales. In turn, this creates an environment suitable for the proliferation of the amoeba in the human intestinal lumen [125]. Lactobacillus postbiotics inhibited the *in vitro* growth of *E. histolytica* HM1-IMSS [126]. Redox proteomics revealed that Lactobacilli (acidophilus) induced the oxidation of several vital amebic enzymes involving pyruvate: the lectin Gal/GalNAc, ferredoxin oxidoreductase, and cysteine proteases. So far, parasite trophozoites have shown reduced binding to the mammalian host cells. Hence, Sarid *et al*. (2022) [127] determined L. acidophilus as a prophylactic probiotic against *E. histolytica* infection.

Conclusions

Host-microbiota interactions evolve immune homeostasis that comprises P2X7 activation and inflammasome triggering. P2X7R influences various immune cells, such as effector T cells, TFH cells in the Peyer's patches, B cells producing SIgA, Th17 cells, and Tregs. These changes enhance protective immunity and regulate local and systemic immune responses. The review was also exposed to microbe-microbe interactions that may affect the outcome of parasitic diseases. Microbiota-parasite interaction involves complex direct and indirect interactions. Direct microbe-microbe interactions affect the physical structure of the mucosal barrier, due to alterations in the chemical composition and productivity of mucin, turnover of the intestinal epithelial cells, and direct competition for nutrients and bactericidal protein production. Direct microbe-microbe interactions involved the predation theory, bactericidal protein production, and overlapping of nutrient resources. In the third section, we exhibited models of collaborative interfaces between host, parasite, and microbiota. Parasites modify immune responses by influencing toll-like receptor expression, altering host antimicrobial peptide production, and activating inflammasomes. These interactions have potentially debilitating effects on gut-dwelling microbes and induce dysbiosis. Yet, the presented biotherapy trials have shown promise in rectifying host immunity and reducing parasite loads in infections like *Giardia* and *Toxoplasma*. However, probiotic therapeutic effects appeared to occur in a strain-specific pattern of immune-microbe and parasite-microbe interactions.

Future research fields should explore probiotics with nanomedicine for enhanced restoration of intestinal homeostasis, immune responses, and the gut microbiome. Also, investigating the efficacy of biotherapy within the complex interactions among host immunity, parasites, and the microbiota, especially in diseases caused by fibrosis or cancer-triggering parasites like *Clonorchis sinensis* and *Schistosoma haematobium* shows promise for pharmaceutical interventions. Research on probiotics and immune therapy utilizing IgA in parasitic infections should encompass vulnerable patient groups, such as individuals with diabetes, pregnant women, and the extremes of age, to assess their potential benefits and safety. The potential of P2X7R as a therapeutic target should be regarded considering its corresponding biological effects. Finally, we recommend studies that define probiotic strains with promising therapeutic effects in clinical settings.

Author Contributions

MAb, ESE and EAE designed the research study. BEA and MAb, ESE and EAE performed the research. MAl, EAA and FEH participated in funding acquisition, acquisition of data, and resource sharing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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