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REVIEW ARTICLE

Probiotics: an alternative anti-parasite therapy

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Abstract
This paper review about probiotic effects and mechanism of action against the gut and non-gut helminths and protozoan parasites. Gastrointestinal parasitic infections are considered a serious health problem and are widely distributed globally. The disease process which emanates from this parasite infection provides some of the many public and veterinary health problems in the tropical and sub-tropical countries. Prevention and control of the parasite disease is through antihelmintic and anti-protozoan drugs, but, due to the increasing emergence of such drug resistance, eradication of parasite infestation in human and livestock still lingers a challenge, which requires the development of new alternative strategies. The use of beneficial microorganisms i.e. probiotics is becoming interesting due to their prophylactic application against several diseases including parasite infections. Recent studies on the interactions between probiotics, parasites and host immune cells using animal models and in vitro culture systems has increased considerably and draw much attention, yet the mechanisms of actions mediating the positive effects of these beneficial microorganisms on the hosts remain unexplored. Therefore, the aim of the present review is to summarize the latest findings on the probiotic research against the gut and non-gut parasites of significance.

Keywords Probiotics · Gastrointestinal infections · Antiparasitic drug resistance · Immunomodulation

Introduction

Intestinal parasites infecting human and livestock are widely distributed in urban and rural areas of tropical and subtropical countries. The disease process which emanates from this infection provides some of the many public and veterinary health issues. Prevention and control of the disease is through proper hygiene and sanitation and regular mass chemotherapy with anthelmintic and anti-protozoan drugs (Alum et al. 2010). However, due to high rate of post-treatment reinfection and lack of functional vaccines, eradication of these parasites is still a huge problem. Moreover, parasite resistance to antiparasitic drugs have been shown to occur rapidly after their introduction (Fig. 1), thus creation of fresh alternatives is the necessity.

Recently, research on potential therapeutic role of microorganisms such as probiotics in the preservation of human health care from different gastrointestinal disorders unveiled health benefits on the individual. Thus, during the last couple of years there is an increased interest in using probiotics as substitutes for medication. The latter play a role in digestion, production of essential vitamins, secreting antibacterial substances like bacteriocins, absorption of essential ions (Ca, Mg, and Fe), or oxygen peroxide, immunomodulation, and protection of the gastrointestinal (GI) tract via colonization resistance, competitive exclusion of harmful bacteria, modulation of enzymatic activity associated with energy balance, and control of functions in peripheral tissues (Urdaci and Pinchuk 2004; LeBlanc et al. 2017; Dubey and Patel 2018; Plaza-Diaz et al. 2019; Wang and Ji 2019). During the last decade, reports were documented on the use of probiotics to prevent gut and non-gut parasite infections (Travers et al. 2011). Much emphasis is given to the interactions in the gut between bacteria, parasites, and the host immune system (El Temsahy et al. 2015; Del Coco et al. 2016). This article sought to present the use of probiotic bacteria in various aspects of host-parasite relationship and their effects on survivability of the parasite.

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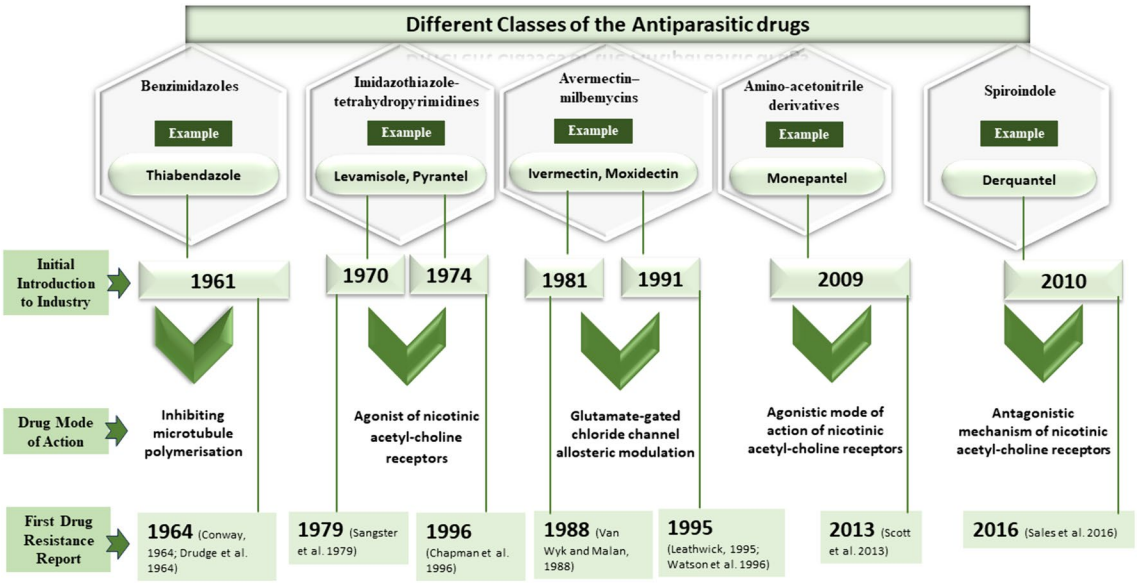

Fig. 1 Types of antiparasitic drugs indicating their year of introduction to industry, mode of action and year of emergence of resistance by parasites

Probiotics and immunity

Probiotics may provide health benefits by modulating the immune response to mount a potential lethal attack during pathogen invasion (Wu et al. 2019). In the gastrointestinal tract, probiotics coordinate with the gut epithelial cells such as, Peyer's patches, M-cells and host immune cells which leads to an increase in the number of cells that produce IgA, IgM and secretory IgA (Szajewska et al. 2001). Furthermore, probiotics can also influence dendritic cells which leads to differentiation of T-regulatory lymphocytes or T-helper cells (Th1, Th2) and modulate cytokine production such as TNF-α IFN-γ and IL-10, IL-12 in managing the delicate balance between required and immoderate defence mechanisms (Resta–Lenert and Barrett 2006; Kaji et al. 2018).

Mechanism of action of probiotics

Probiotics act against parasites by enhancing the population of beneficial microorganisms, such as bifidobacteria and lacto-bacilli, which show competitive exclusion against harmful pathogens in the intestine. Another mechanism is secretion of antibacterial agents, such as bacteriocins, and some organic acids like lactic, butyric and acetic acid, that might have antiparasitic activity (Chiodo et al. 2010; LeBlanc et al. 2017; Hernández-González et al. 2021). Probiotics primarily promote host immunological response and immunomodulation of either the innate or adaptive immune system, and these modulations are brought about both locally and systemically (Fig. 2).

There are limited experimental reports of probiotics in treating parasite infections, and also there are no clinical trials, therefore most of the research work described was developed in different animal models (typically mouse) and susceptible animals (Table 1). In this review we will present experimental and epidemiological evidences on the impact of probiotics on a variety of protozoan and helminth parasites.

Probiotics against protozoan parasites

Giardiasis

This intestinal infection is caused by a flagellated protozoan parasite *Giardia lamblia* which adhere to human intestinal epithelium and infect 280 million people per year (Ankarklev et al. 2010). The host response through T cells, neutrophils, antibodies IgM, IgA and IgG as well as macrophages are reported to take a significant role in the control of Giardiasis (Hawrelak 2003). Therapeutic techniques using probiotics to restore the normal gut microbiota was reported to either prevent or treat Giardiasis (Ventura et al. 2018). Oral intake of *Saccharomyces boulardii* by gavage 15 days prior to infection and 22 days thereafter dramatically lessen the parasite load (70% reduction), improve intestinal height of villi and depth of crypts, increase mucus production, and increasing the quantity of intraepithelial goblet cells

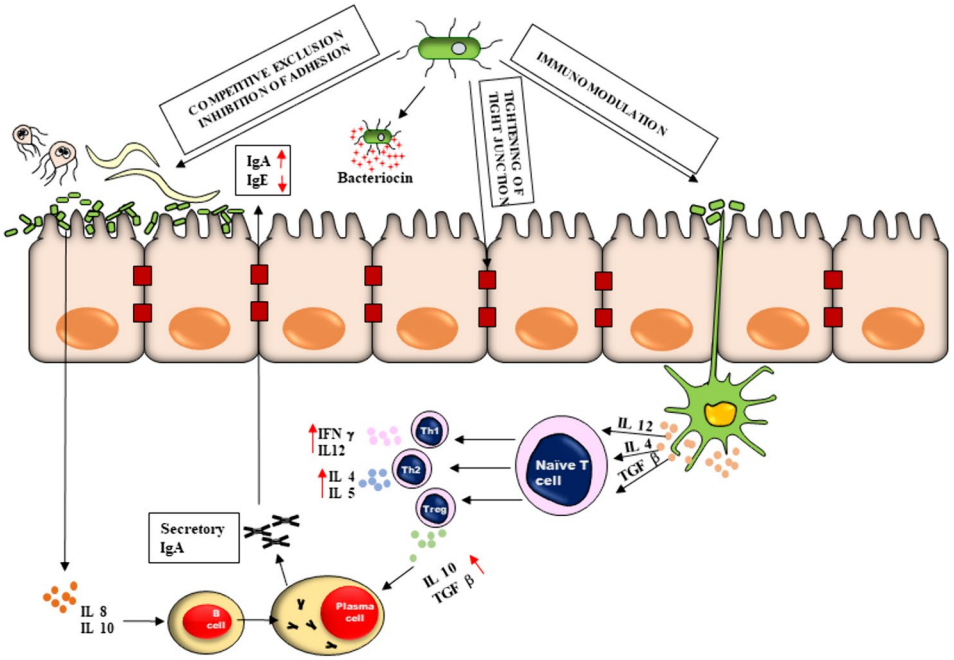

Fig. 2 Mechanism of action of probiotics to control pathogens in the gut. The four major factors are, (i) competition for adhesion and nutrients, (ii) secretion of antimicrobial substances like lysozymes and bacteriocin, (iii) tightening the intracellular junction between cells thus enhancing the barrier and (iv) modulation of immune response through cellular response that includes the differentiation of T cells and humoral response includes development IgA secreting plasma cells

Table 1 List of probiotics tested on different eukaryotic parasites in vivo and in vitro

Pathogen	Probiotics/ probiotic supplements tested	Host	References
Ascaris suum	*Bifidobacterium lactis* (pig isolate)	Pig	Solano-Aguilar et al. (2004)
Babesia microti	*Lacticaseibacillus casei* ATCC7469	Mouse	Bautista et al. (2005) and Bautista et al. (2008)
Cryptosporidium parvum	*Limosilactobacillus reuteri* 4000, 4020	Mouse	Alak et al. (1997)
	L. reuteri 4000, 4020 or *L. acidophilus* NCFM	Mouse	Alak et al. (1999)
	L. reuteri 4000, 4020	Mouse	Waters et al. (1999)
	Lacticaseibacillus rhamnosus GG + *L. case*	Human	Pickerd and Tuthill (2004)
	i Shirota	Neonatal	Guitard et al. (2006)
	Actimel	Calf	Harp et al. (1996)
	Brevibacillus brevis, Enterococcus faecium, Pseudomonas alcaligenes	Cell culture	Glass et al. (2004) and Foster et al. (2003)
	L. reuteri ATCC23272 or *Lactobacillus acidophilus* NCFM	Cell culture	Foster et al. (2003)
	Bifidobacterium breve ATCC15698 or *Bifidobacterium longum* ATCC15707	Cell culture	Deng et al. (2001)
Eimeria tenella/acervulina	Primalac	Chicken	Dalloul et al. (2003b)
	Mitomax	Chicken	Lee et al. (2007)
	Mitogrow	Chicken	Lee et al. (2007)
	Lactobacillus acidophilus Lb33ac, *Ligilactobacillus salivarius* Lb14c7 Lb16c6	Cell culture	Tierney et al. (2004)
Giardia lamblia	*Lactobacillus johnsonii* LA1	Gerbil	Humen et al. (2005)
	L. casei MTCC1423	Mouse	Shukla et al. (2008)
	E. faecium SF68	Mouse	Humen et al. (2005) and Shukla and Sidhu (2011)
Schistosoma mansoni	*Zymomonas mobilis*	Mouse	Mohamed et al. (2014)
Trichinella spiralis	*L. casei* ATCC7469	Mouse	Bautista et al. (2001) and Kato et al. (1999)
Plasmodium chabaudi	*L. casei* ATCC7469	Mouse	Martinez et al. (2006)
Trypanosoma cruzi	*L. casei* ATCC7469	Mouse	Garfias et al. (2008)
Hymenolepis diminuta	*Lactobacillus taiwanensis* S29, *Lactiplantibacillus plantarum* S27	Rat	Mandal et al. (2024)

lymphocytes (Ribeiro et al. 2018). The first primary study on *Lactobacillus johnsonii* La1's ability to protect against *G. lamblia* in vivo, in which rats were given with probiotics 10^8 CFU for seven days before trophozoite injection, exhibited no morphological damage to the intestinal epithelium, and the population of trophozoites stage reduced dramatically (Humen et al. 2005). In another study in Gerbils, daily treatment of 10^9 CFU *Lactobacillus casei* for 30 days decreased trophozoites population, shortened the duration of an infection by 14 days, and shielded the mucosa from parasite-caused damage (Shukla et al. 2008). A comparative study was reported in two groups of *Giardia* infected mice, one feeding with probiotics showed architecture of normal microvillus and increased variety of goblet cells, whereas the other untreated group showed severe microvillus atrophy, oedema, vacuolate animal tissue cells, and inflammation (Shukla et al. 2012). The efficacy of four bacterial strains *Lactobacillus acidophilus*, *L. casei L. rhamnosus* GG (LGG) and *L. plantarum* in the regulation of murine Giardiasis reported a reduced duration of the *G. lamblia* cycle, enhanced cyst removal rates and decreased trophozoites in the colon, resulting to disease prevention (Goyal et al. 2011). Treatment with probiotic LGG (1×10^9 Lactobacilli/0.1 mL) orally to Giardia-infected mice, restored the gut's microbes and modified the immune response of the mucosa, a significant rise in the specific secretory IgA antibody, CD4 + T lymphocyte, IgA + cells, and, cytokines IL-6 and IL-10 were reported (Goyal and Shukla 2013). It was also reported that animals fed with probiotics demonstrated a substantial rise in intestinal disaccharidases, superoxide dismutase, and antioxidants and lower the levels of oxidants in the small intestine, indicated that LGG has antioxidative activity (Goyal et al. 2013).

Giardia-infected mice when given probiotic LGG (10^9/0.1 mL) orally, improved the balance of the gut microbiota, reduced the production of cytotoxic CD8 + T cells and cytokines including IL-10 and IL-6, and secreted IgA antibodies to control the mucosal immunological response, and increasing the number of IgA + cells and CD4 + T cells in the lamina propria (Amer et al 2014). Probiotics *L. acidophilus* (P106) have shown to act on the parasite directly by altering the trophozoite's cellular structure i.e., disorganizing the cytoplasm, cell membrane, and sticky disc. Bacteriocins generated from this probiotic as well as from *Lactobacillus plantarum* (P164) inhibit the adherence and lower the trophozoites number by about 58% and improved intestinal pathology (Amer et al 2014). The extracellular bile-salt hydrolase (BSH) like effects of *L. johnsonii* La1 reduced the growth of *Giardia duodenalis* in vitro by creating deconjugated bile salts (Travers et al. 2016). Further study, the BSH-like traits of *L. johnsonii* La1 and *L. gasseri* CNCM I-4884 showed expression ofe BSH47 and BSH56 genes respectively that might be responsible for anti-Giardia properties (Allain et al. 2018). The probiotic bacteria *Lactobacillus helveticus*, *L. acidophilus* and *Bifidobacterium bifidum* have also been reported as safe and effective treatments for Giardiasis, curing an infection rate of 87.5% (Al-Megrin et al. 2021). As a consequence of their direct effects on the parasite as well as their antioxidant and immunomodulatory properties, probiotics are a secure and beneficial method for treating and preventing *Giardia* infection, whether used alone or in combination with antiprotozoal drugs.

Eimeriasis or Coccidiosis

It is a disease of poultry and livestock caused by an apicomplexa parasite *Eimeria* which create huge loss of economy (Lee et al. 2007). Sporulated oocysts are the infective stage of the parasite which gets transmitted through contaminated food and excyst in the upper lumen of intestine to sporozoites and further undergo asexual reproduction to produce innumerable merozoites that invade other epithelial cells and recruit second schizogony (Shirley et al. 2005). Though several drugs such as halofuginone, monensin lasalocid, amprolium and live vaccines are available to treat Eimeriasis, yet new strategy to control the infection is much needed due to parasite resistance to drug and recurring of virulence in the case of live vaccinated host (Allen and Fetterer 2002). Primalac (commercially available *Lactobacillus* based product) stimulates chicken intestinal intraepithelial lymphocytes that led to a substantial decrease in the number of *Eimeria acervulina* oocysts and enhance immunity in birds (Dalloul et al. 2003a; Dalloul et al. 2003b). Other workers also showed significant escalation in cytokine (γ-IFN and IL-2) levels together with a reduction in oocyst shedding when dose of Primalac was doubled thus indicating an immune stimulation mediated protection level (Dalloul et al. 2005). Another study reported in chicken-treated *Lactobacillus* strains Lb16c6 slowed invasion of the parasite, presumably due to spatial interference or competitive exclusion (Tierney et al. 2004). *Bacillus subtilis* and anticoccidial herb work well together to decrease the excretion of oocysts and the level of IL-17A mRNA (Yang et al. 2021). However, dietary antibiotic and probiotic treatments had little effect on *Butyricicoccus pullicaecorum*, *Subdoligranulum variabile* and *Sporobacter termitidis* gut microbial diversity following cocci challenge (Jia et al. 2022). Another set of findings demonstrated for the first time that probiotic alone and probiotic with herb *Bidens pilosa* enhance the gut health of chickens infected with *Eimeria* by triggering an increase in functional abilities of tight junction proteins, pro-inflammatory cytokines, and antioxidant enzymes (Memon et al. 2021). At doses of $1.5X10^8$ CFU/ml and $3.0X10^8$ CFU/ml, the probiotic *Pediococcus pentosaceus* ABY 118 can be utilized to prevent broiler chickens infected with *Eimeria tenella* oocysts from developing high levels of ChINF-c and

ChIL-10 (Yulianto et al. 2021). Selenium-enriched probiotic supplements had significant benefits on improving chicken growth performance, antioxidant capabilities, mRNA gene expression, decreased oocyst shedding, and cecal lesion scores as well as protecting against *E. tenella* (Mengistu et al. 2021).

Amoebiasis

Amoebiasis is one of the most frequent protozoan diseases in developing countries that is caused by enteric protozoa *Entamoeba histolytica* and about 50–60% of the infected population are asymptomatic. This parasite is commonly found in the gut and cause physiological disturbance or immuno-compromise, causing diarrhoea, bloody stools, and perhaps invading other organs if left untreated, including amoebic liver abscess, which becomes fatal (Huston and Petri Jr 2001; Mortimer and Chadee 2010). The transmission of infective cystic stage is via faecal-oral route and transform to trophozoites in the host's intestine which adhere to the colonic mucin layer with Galactose and N-acetyl-D-galactosamine (Gal/GalNAc)-specific lectin (Haque et al. 2003). Common drugs used for treatment are metronidazole and tinidazole, however new therapies are needed in the face of rising antibiotic resistance. In a study conducted by Sarjapuram et al (2017) five probiotic bacterial strains were individually co-culture with *Entamoeba,* demonstrated a substantial reduction in parasite survival of up to 71%. Furthermore, *Lactobacillus* postbiotics inhibitory action to trophozoite population was reduced by 56% (Cuellar-Guevara et al. 2019). A positive impact of oral consumption of probiotic *Saccharomyces boulardii* in acute Amoebiasis in combination with antibiotics was reported to reduce the duration of amoebic symptoms and the number of cysts present in stools (Mansour-Ghanaei et al. 2003). Another in vitro study demonstrated that the oxidation of essential proteins in *E. histolytica* caused by *L. acidophilus* generation of H2O2 leads to death of the parasite (Sarid et al. 2022). *Entamoeba dispar*'s ability to induce amoebic lesions is inhibited by another lactic acid bacteria *Weissella paramesenteroides* WpK which increases the caecal mucosa's barrier function, though it is yet unclear how these probiotics combat the parasite (Prado et al. 2020).

Cryptosporidiosis

Another human intestinal protozoan parasite *Cryptosporidium*, causes diarrhea and life-threatening gastrointestinal infections in immunocompromised individual. *Cryptosporidium* oocysts entered through oral route to the small intestine where mobile sporozoites are released and penetrate the epithelial cells of the gastrointestinal tract. The sporozoites infiltrate host cells to create their own intracellular niche, where they locally damage the microvilli and increased ion secretion and reduced Na + and H_2O absorption. Although there is a real risk of water-borne Cryptosporidiosis outbreaks, yet there is unavailability of fully effective treatment. A study showed that *Cryptosporidium* susceptibility is enhanced in immunocompetent mice but when such mice were treated with *Lactobacillus reuteri* (strains 4000 & 4020) or *L. acidophilus* NCFM, *Cryptosporidium* oocyst shedding got reduced (Alak et al. 1999). Some study documented a long-term resolution of Cryptosporidiosis in a 12 years old girl following *Lactobacillus GG* and *L. casei* treatment where nausea and diarrhoea totally disappeared within 10 days post therapy, stomach discomfort decreased and no oocysts seen in the stool sample four weeks post treatment (Pickerd and Tuthill 2004). In vitro investigations revealed that cell-free supernatants of *Lactobacillus reuteri* strain 23,272, *L. acidophilus* NCFM, *Bifidobacterium breve* and *B. longum* resist the viability and infectivity of *C. hominis* and *C. parvum* (Foster et al. 2003; Glass et al. 2004). In immunocompromised individuals, probiotic *L. reuteri* has been described as a very successful therapy for Cryptosporidiosis (Fahmy et al. 2021). The alkaline medium is required for the parasite *Cryptosporidium* excyst but the acidity of lactic acid bacteria may hinder this process and reduce its viability (Smith et al. 2005; El Temsahy et al. 2015). The effects of probiotic *L. rhamnosus* GG in Indian children with *Cryptosporidium* diarrhea observed benefit children's gut health on intestinal function, clinical outcomes and the immunological response after treatment limit the injury (Sindhu et al. 2014). A significant reduction in *C. parvum* burden when treated with probiotics bacteria, was demonstrated that daily treatment with a combination of *Lactobacillus plantarum* and *L. acidophilus* lower the *Cryptosporidium* parasite infection in mice and rats compared to the untreated group (Sanad et al. 2015; AL-Khaliq et al. 2021). The impact of widely used commercial clove oil (*Syzygium aromaticum)*, *L. acidophilus* LB, dill seed oil (*Anethum graveolens)* and zinc as alternative therapies in experimental mice that had been exposed to *C. parvum* showed oocysts reduction rates by 98.3% in the zinc-treated mice and 95.77% in *L. acidophilus* LB and dill-treated groups, while 91.55% was observed in anti-*Cryptosporidium* drug NTZ (nitazoxanide) treated group (Gaber et al. 2022).

Trichomoniasis

Trichomoniasis is a sexually transmitted disease (STD) caused by a protozoan parasite *Trichomonas vaginalis* (CDC 2021). Trichomoniasis, can induce vaginal irritation, making it easier to transfer the virus on to a sexual partner. A published work documented that probiotics therapy induced a reduction of inflammatory response and substantial changes in the vaginal physicochemical parameters (lower pH values,

higher redox potential) in *T. vaginalis* infected women. However, in combination with metronidazole, the antibacterial activity of the drug alters, enhancing the efficiency of *T. vaginalis* treatment in the presence of bacterial vaginosis (Sgibnev and Kremleva 2020).

Trypanosomiasis

Trypanosomiasis is another protozoan infection caused by *Trypanosoma* spp in humans and animals, causing American Trypanosomiasis or Chagas disease, caused by *T. cruzi* and the African Trypanosomiasis or Sleeping sickness caused by *T. brucei*. *T. cruzi* is believed to impact 6 to 7 million individuals globally, predominantly in South America (WHO 2021). In Sub-Saharan Africa, Trypanosomiasis is still a serious problem for animal health (Ishaku et al. 2019). Anaemia, leukopenia, serum biochemical abnormalities, and oxidative damage are all common outcome, caused during the disease and immunosuppression (Namangala 2011; Reddy et al. 2016; Eze et al. 2016; Nweze et al. 2017). Increase in IgM parameter in blood serum, explicit for antigens like xenogeneic erythrocytes and bacterial lipopolysaccharide are a portion of the immunological dysfunctions as well as inhibition of both T and B lymphocyte activities during infection (Vincendeau and Bouteille 1996; Barry and Carrington 2004; Namangala 2011). Homidium, isometamidium and diminazene aceturate are the most widely used trypanocides (Giordani et al. 2016). Probiotics *Saccharomyces cerevisiae* therapy was reported in *T. brucei brucei* infected rats, which increased the level of antibody titre in the host and parasitaemia was significantly reduced (Eze et al. 2012). Another study reported treatment of *T. cruzi* infected NIH mice with *L. casei* reduced the number of parasites [Garfias and María del 2008], and a combination of probiotic with diminazene aceturate, the infection got cleared, and the clinical pathological changes in the serum (creatinine levels, ALT, BUN, AST) antioxidative ability, or haematological indices become insignificant (Okolo et al. 2019).

Leishmaniasis

Leishmaniasis is caused by an intracellular protozoan parasite *Leishmania* spp. and affects the visceral organs, usually spleen, liver, and bone marrow. An estimated 700,000 to 1.2 million new cases of cutaneous Leishmaniasis are diagnosed each year and annual new cases of 100,000 visceral Leishmaniasis were observed (CDC 2020). More than 20 different *Leishmania* species can infect humans, of which *L. donovani* is the most dominant and causes more severe diseases.

The elimination of the *Leishmania* parasite is dependent on the active of type I immune action, which are characterized by the initial Interleukin-12 (IL-12) production, activation of macrophages and T helper-2 (Th2) response and the production of cytokines including IL-4 increases (Costa et al. 2012). Due to the toxicity of existing drugs for visceral Leishmaniasis, coupled with lack of vaccine and immunomodulation therapy, alternative strategy is urgently required (Maurya et al. 2016). One study revealed that kefir grain (a complex probiotic) treatment for 21 days on daily basis in infected mice stimulates macrophages to boost phagocytosis, along with increase in nitric oxide (NO) and cytokine production particularly pro-inflammatory cytokines which ultimately resulted in increased Th1 polarisation and decreased Th2 polarisation (Ali et al. 2016).

Malaria

Plasmodium protozoan parasite is the causative agent of the vector-borne illness Malaria. This poses a threat to around 3.3 billion people worldwide (Sinha et al. 2014). With emerging resistance to the Malaria drug chloroquine and no availability of licensed vaccine, prevention of the disease is primarily based on chemotherapy and vector control measures (Martin et al. 2009). In recent years, there has been a lot of research on the use of gut bacteria for Malaria preventative methods. *Plasmodium* in the midgut can be directly harmed by bacteria, either by establishing physical barriers that resist the parasite to reach the epithelium, or by producing antiparasitic compounds, like reactive oxygen intermediates (Cirimotich et al. 2011a, b). The gut microbiota, on the other hand, reduce parasite infection by activating the innate immune response of the mosquito to produce antimicrobial compounds like cecropins, gambicin and defensins which work against both bacteria and parasite. Moreover, the number of infected mosquitoes considerably decreased when different bacterium species were co-infected with *Plasmodium* (Gonzalez-Ceron et al. 2003; Dong et al. 2009; Cirimotich et al. 2011a, b; Ramirez et al. 2014). As a result, the midgut microbiome has been shown to have effects of probiotics on mosquito immunity to parasitic infection, making it a prospective tool for blocking transmission. Human gut pathobiont *Escherichia coli* O86:B7 aids immunological protection against Malaria indicated for the first time a favourable effect of human gut probiotics on Malaria immunity. The glycan Gala1-3Galb1-4GlcNAc-R (a-gal) found on the surfaces of E. coli O86:B7 and *Plasmodium* sporozoites, whereas a-gal production is reduced in humans by deletion of the corresponding gene a1,3GT (Yilmaz et al. 2014; Galili and Swanson 1991). As a result, people can produce anti-a-gal antibodies that protect them, with up to 5% of the circulating immunoglobulin IgM and IgG repertoire directed against this glycan (Macher and Galili 2008).

Probiotics against helminth parasites

Schistosomiasis

Schistosomiasis is the 3rd most destructive neglected tropical disease and is widely distributed in tropical and subtropical countries with 3.31 million disability-adjusted life per year (DALY) (Hotez et al. 2014). More than 258 million individuals are infected in 78 countries, 92% of whom reside in Africa (WHO 2016). In chronic situations the parasite alters the function of the urinary bladder, liver, spleen, gut and lungs (CDC 2016a). In children, Schistosomiasis affects the mental and physical growth while in adults it reduces their ability to work. Praziquantel has been administered so far as a mass drug but lately its resistance by the parasite has been reported (Stothard et al. 2013). Several probiotic strains have been studied and documented including *Zymomonas mobilis*, *Lactobacillus delbrueckii* subsp. *Bulgaricus*, *Streptococcus salivarius* subsp. *Thermophilus* and several *Lactobacillus* species as well as probiotic Labneh (yogurt cheese) against Schistosomiasis. *Lactobacillus sporogenes* is one of the most widely investigated probiotic strains with an anti-schistosome activity against cytokine induced apoptosis in *Schistosoma mansoni* and decreased the chances of DNA damage and chromosomal abnormalities in infected mice (Zowail et al. 2012; Mohamed et al. 2014). Using *L. sporogenes* along with praziquantel therapy helps to treat the hepatic illness and intestinal damage brought on by *Schistosoma* parasite (Mohamed et al. 2014). The genetically modified *Escherichia coli* Nissle 1917 (EcN-Sj16) is a unique engineered probiotic with potential for treating inflammatory bowel disorders in colitis infection (Wang et al. 2021a, b). A preventive effect by probiotics (*L. delbrueckii* subsp. *bulgaricus* DSM 20080 and *L. acidophilus* ATCC 4356) and yogurt has been reported to reduce oxidative stress and liver fibrosis in mice infected by *S. mansoni* (El-Khadragy et al. 2019).

Trichinellosis

Trichinellosis is one of the top ten food-borne parasite diseases in the world, posing a public health risk as well as financial loss in pig production and food safety (Gottstein et al. 2009). More than 55 countries in the world have reported Trichinellosis, and it is estimated that about 10,000 cases occur each year (Murrell and Pozio 2011). In human the disease is characterized by enteritis (intestinal stage) and inflammation of skeletal muscle tissue, accompanied by degenerative change of tissue/muscle stage. The development of larval capsules and host immune suppression are primarily responsible for *Trichinella spiralis* infection and can be regulated by serine proteases in the intestine and muscle of adult and neonatal larvae (Bruschi and Chiumiento 2011; Wu et al. 2013). Parasites also alter the function of dendritic cells, possibly leading to regulatory T and B-cells' immunosuppression, release cytokines and activated macrophages (Aranzamendi et al. 2013). Anthelmintics are only effective against mature worms, and there is no successful vaccine (Ortega-Pierres et al. 2015). In multiple studies, effects of bacteriocin-producing bacterial strains and probiotics were used on *T. spiralis*. Another strain *L. plantarum* P164, was demonstrated to be 90% effective against *T. spiralis* (El Temsahy et al. 2015). In addition to their anthelmintic effect, most of the probiotic strains acted on innate immune system during phagocytosis. *Lactobacillus fermentum AD1*, *Enterococcus durans ED26E/7* and *L. plantarum17L/1* have the strongest stimulating effects on the phagocytic activity of blood leukocytes and monocytes as well as enzymatic action (Dvorožňáková et al. 2016). Other probiotic strains promote the development of IgA and IgG anti-*T. spiralis* antibodies, which aid in the maintenance of intestinal humoral immune response by sticking to antigens and inhibiting epithelial adhesion (Martínez-Gómez et al. 2011). One study supported that the probiotic strains *L. plantarum* 17L/1 and *L. fermentum* CCM7421 act as efficient mediators to control macrophage oxidative metabolism during *T. spiralis* infection (Vargová et al. 2020). A study found that expressing mIL-4 in *L. plantarum* NC8 significantly boost humoral, cell-mediated and mucosal immune responses in mice against *T. spiralis* (Wang et al. 2020). Another advanced discovery revealed that oral vaccination of mice with pValac-Ts-ADpsp/pSIP409 delivered by invasive *L. plantarum* induced anti-Ts-ADpsp-specific IgG production and enhanced the cellular and mucosal immune responses, alleviating intestinal damage and lowering worm burden. (Xue et al 2022). Further treatment of *T. spiralis* encysted larvae with albendazole was greatly enhanced by *L. acidophilus* (Bocktor et al. 2022). After probiotic therapy, there was a beneficial modification of the host intestinal immune response in *T. spiralis* infection, lamina propria lymphocytes (LPL) and intra-epithelial (IEL) subpopulations increase (Emilia et al. 2019). *L. paracasei* CNCM and *L. casei* ATCC 393 have an effect on the growth of the intestinal phase of *Trichinella britovi*, albeit, however the precise mechanism regulating this action is not widely explored (Boros et al. 2022). Nucleic acid vaccine given by invasive *L. plantarum* presents a fresh strategy for *T. spiralis* prevention (Xue et al. 2021). *L. plantarum* NC8 dependent vaccine induce mucosal, cellular and humoral immune responses and protect against various phases (muscle larva and adult worms) of *T. spiralis* infections in BALB/c mice, making it a potentially effective oral vaccine candidate for Trichinellosis (Wang et al. 2021a, b).

Toxocariasis

Roundworm-borne Toxocariasis is a widespread parasitic infection that is often undiagnosed and found worldwide with prevalence rates of up to 40% or higher in some areas (CDC 2016b). Human can become infected by consuming uncooked or undercooked meat from an infected host such as ruminants, chickens, pigs (Taira et al. 2004; Smith and Noordin 2006). In the host intestine, the eggs hatch up to larvae and penetrate the wall and spread through the bloodstream to various organs and tissues (Fan et al. 2004). The Ocular Larva Migrans (OLM) and Visceral Larva Migrans (VLM) are the two most prevalent classical types of illness (Pecinali et al. 2005). Other types of Toxocariasis, such as Covert Toxocariasis (CT), asthmatic Toxocariasis and neurological Toxocariasis, have also been reported (Chiodo and Basualdo 2008). Human Toxocariasis is difficult to treat due to its different clinical form (Smith and Noordin 2006). New alternatives, such as probiotics, have been reported in infected mice treated with 3×10^8 (CFU/ml) *Enterococcus faecalis,* significantly reduced the worm count. In addition, *E. faecalis CECT71219* showed larvicidal activity in mice after injection at various doses of 7×10^4 (CFU/g), cultured 1.46×10^6 CFU and 1×10^8 CFU (Chiodo et al. 2010). The final effect of supplementing *S. boulardii* with a dose of 1×10^7 (CFU/g), resist the severity of infection in mice (De Avila et al. 2016). Another probiotic *Saccharomyces boulardii* can also regulate mRNA expression levels in mice, especially IFNγ and IL-12. This study showed that administering *S. boulardii* as a probiotic might help reduce the risk of developing visceral Toxocariasis (Cardoso et al. 2020). The probiotic *L. acidophilus* ATCC 4356 decreased the severity of *Toxocara canis* infection in mice, but it had no direct impact on larvae, showing that the probiotic must interact with the host in order to have a positive effect (Cadore et al. 2021).

Ascariasis

It is a roundworm infection caused by *Ascaris lumbricoides* in human and occurs mostly in tropical and subtropical regions (Bethony et al. 2006; Walker et al. 2011). Deliberating its worldwide distribution and huge effect on economy and public health, suitable invasive manipulate approaches are necessary to manipulate *Ascaris* infections. *Bifidobacterium lactis* subsp. *animalis* and *L. rhamnosus* has been mentioned as probiotics for *A. suum* (Solano-Aguilar et al. 2009; Thomas et al. 2011; Jang et al. 2016). These probiotics reduced eosinophil activity and the intensity of allergic skin and lung symptoms caused by *A. suum* infection. As a result, these research procedures might be utilised to verify the influence of different probiotic strains on pathogen responses in order to combat *Ascaris* species drug resistance. *Bifidobacterium animalis* subsp. *lactis* increased parasite-specific IgG1, IgG2 and IgA responses in pigs with *A. suum* infections, reduced small-intestinal eosinophilia, and improved intestinal glucose absorption (Solano-Aguilar et al. 2018). A paraprobiotic's (dead probiotic's) ability to cure *Ascaris* infection is due to the production of Cry5B protein from *Bacillus thuringiensis* known to have anthelmintic properties (Urban et al. 2021). When probiotics containing *S. boulardii* was given, the dysbiosis index reduced in patients having difficult therapy for concurrent *Giardia* and *Ascaris* invasions (Protsyk 2019).

Trichuriasis

Apart from Ascariasis, Trichuriasis is another common nematode infection infecting about 800 million people and other mammalian hosts (CDC 2016c). It continues to be a public health issue because it imposes a significant economic burden on many individuals in developing nations and reduces the quality of life (Pullan et al. 2014). Parasites spread from person to person through ingestion of eggs with food or water (PAHO 2003), and the infected people are mostly asymptomatic or may be accompanied by mild diarrhea. Regular deworming with anthelminthic medicines like mebendazole and albendazole, as well as strict cleanliness practices, may help to reduce infections. However, due suboptimal dosage, breeding grounds for drug resistance increases, therefore, elimination of Trichuriasis requires specific treatment strategies, such as probiotics that can stimulate immune system. Several studies have determined the impact of oral intake of *L. rhamnosus (JB-1)* in *Trichuris muris* resistant C57BL/6 mice, elevated IL-10 levels and increase the number of mucus secreting epithelial cells (Summers et al. 2005). In contrast, oral ingestion of *L. casei* ATCC 7469 increased susceptibility to *T. muris* infection (McClemens et al. 2013). This was linked to a down-regulation of the Th1 immune response, which was defined by low levels of IFN-γ, and a down-regulation of the Th2 immunological response, characterized by lower levels of IL-4 and IL-13 (Dea-Ayuela et al. 2008).

Haemonchosis

One of the most significant parasites in terms of economic impact that affects small ruminants globally is *Haemonchus contortus*. It is a blood-sucking nematode that mostly affects cattle, sheep, and goats. It feeds on the blood from capillaries in the abomasum of ruminant animals. Animals with severe cases of the nematode infection may have anemia, weight loss, or even death. To control the infection a study was reported that kefir (a complex probiotic) prepared from camel, goat, ewe, and cow milk has anti-parasitic effects in vitro against *H. contortus* in sheep. As a result, kefir offers

a viable alternative to conventional anthelmintics in the treatment of Haemonchosis (Alimi et al. 2019). An advanced study done by Yang et al. 2020, reported that constructed recombinant *Bacillus subtilis* named rBS$^{CotB-HcG}$ express the glyceraldehyde-3-phosphate dehydrogenase of *H. contortus* (HcGAPDH) on its recombinant bacterial spore are coat protein B (CotB) as a carrier. A recombinant *B. subtilis* expressing a fusion protein CotB-HcGAPDH on its spore's surface that induces both cell-mediated and humoral responses and protects sheep against *Haemonchus* infection (Yang et al. 2020). The naturally occurring protein *Bacillus thuringiensis* (Bt) crystal protein 5B (Cry5B), produced by a bacterium, has a significant potential to improve existing methods of preventing *H. contortus* infections in sheep and overcoming parasite resistance to drugs currently employed to control this significant ruminant parasite (Sanders et al. 2020).

Hymenolepiasis

One of the most prevalent intestinal tapeworm infections in humans, Hymenolepiasis is brought on by worms belonging to the family Cestoda, genus *Hymenolepis*, species *H. nana* and *H. diminuta.* An estimated 50–75 million carriers of Hymenolepiasis globally and children under the age of 15 have the highest frequency of infection (Ikumapayi et al. 2019). The administration of two probiotics *L. taiwanensis* strain S29 and *L. plantarum* strain S27 with 10^9 CFU/mL to *Hymenolepis diminuta* infected rats reduced egg per gram (EPG) in faeces as well as worm burden in the intestine (Mandal et al. 2024). Probiotics can suppress the establishment of infection in the intestine of rats. Improvement of total body weight and intestinal weight were observed. Similarly, significant level of amelioration was seen in hemoglobin, RBC and WBC count and biochemical parameters of the host after treatment. These two probiotics remodelled the morphology and cellular configuration of intestinal microvilli and epithelium with a great recovery of mitochondrial density in the intestinal tissue (Mandal et al. 2024).

Conclusion

This new substitute control strategies by probiotics becomes clear that they have the potential to inhibit the spread of eukaryotic infections and help reduce the risk of overspreading of certain parasites. There are differences in the effectiveness of the probiotic strains, which can be explained by the variability of the study design, the test animals used, the dosage range, and the route of administration. The results of these experiments showed that in repeated clinical studies in humans and animals, some strains of *Lactobacillus* and *Enterococcus* can be used as probiotics for the prevention or treatment of parasites. Its mechanism can be strain-specific or by a combination of several mechanisms. Moreover, most of the results of probiotics on protozoa and helminths have been pronounced in animal experiments and in vitro way of life. In some cases, there are almost no human research reports that have evaluated the interaction of parasites with microbes, and the molecular mechanisms by which these beneficial microbes work on animal models are still poorly understood. As a result, more research utilizing current molecular methods on host-microbe or microbe-pathogen interactions might help us to better understand how probiotics work.

The intricate interconnections between the human body, gut microbiota, and parasites create a complex ecosystem in which changes in one component trigger a reaction in the others. Thus, an in-depth understanding of the current infection decision process is required. This approach involves taking complex, interdisciplinary, and comprehensive measures. Many unanswered questions remain, such as the existing interactions between the microbiota, intestinal parasitic diseases, immune response and inflammatory processes as well as the mechanisms underlying how probiotics act against intestinal parasites and the potential therapeutic use of probiotics in humans. Finally, new and intriguing fields such as the research of the parasitome and metabolome of gut microbiota during chronic parasite infection, as well as their interaction with host immune regulatory systems, provide the foundation of an integrated approach.

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Declaration

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