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Functional Food for the Stimulation of the Immune System Against Malaria

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Abstract

Drug resistance has become a threat to global health, and new interventions are needed to control major infectious diseases. The composition of gut microbiota has been linked to human health and has been associated with severity of malaria. Fermented foods contribute to the community of healthy gut bacteria. Despite the studies connecting gut microbiota to the prevention of malaria transmission and severity, research on developing functional foods for the purpose of manipulating the gut microbiota for malaria control is limited. This review summarizes recent knowledge on the role of the gut microbiota in malaria prevention and treatment. This information should encourage the search for lactic acid bacteria expressing α-Gal and those that exhibit the desired immune stimulating properties for the development of functional food and probiotics for malaria control.

Keywords Alpha gal · Antibody · Gut microbiota · Lactic acid bacteria · *Plasmodium* · Probiotics

Beneficial Microbes: an Alternative for the Control of Infectious Diseases

Infectious diseases pose a challenge to human health and modern society. In particular insects such as mosquitoes and sand, flies are considered the most important vectors of human diseases, while ticks are second to mosquitoes in humans and are the most important vectors of animal diseases. Mosquitoes and ticks are responsible for the transmission of pathogens that cause diseases such as malaria and dengue [1], Lyme disease, and babesiosis [2], respectively. Cholera and tuberculosis that are non-vector borne jointly contribute to the huge burden of death from infectious diseases [3]. In order to mitigate this effect, prevention and control have focused on vector control [4], antimicrobial drugs, and development of vaccines [4, 5]. More recently, the role of gut microbiota for the control of infectious diseases, including viral diseases such as Covid-19, is being elucidated [6–11]. In consequence, the interest in probiotics as an alternative to antibiotics and other antimicrobial drugs is timely due also to increase in antibiotics resistance [12]. Especially, antimalarial resistance [4, 13] has become one of the major twenty-first century medical problems which are affecting the efforts to reduce mortality by infectious diseases [3, 8, 14, 15].

The United Nations sustainable development goal included on their second agenda the provision of safe, nutritious, and sufficient food while the third agenda focuses on promoting good health and well-being for all at all ages [16]. In the process of providing more food, functional food should also be considered. Such food, while being included to tackle hunger, will at the same time function as a means

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to deliver prophylaxis [8, 17, 18]. Traditionally fermented food contains beneficial microbe and may serve as a source of lactic acid bacteria [17, 19–22] with properties useful for immune improvement and potentially the prevention and/or treatment of malaria [6, 7, 23–25].

Fermented Food as a Source of Probiotic Lactic Acid Bacteria

Lactobacilli are the groups of bacteria widely used for probiotics [26–28] due to their functional properties [15, 29, 30]. The preference for lactobacilli from fermented food is associated with their ability to multiply at low pH [28, 31], survive the intestinal bile [27, 32, 33], compete for adhesion site [34–36], out-compete and limit the growth of pathogenic bacteria [32, 37, 38], and also regulate the immune system [8, 15, 29, 39, 40].

The ability to modulate both innate and adaptive immune responses is one of the major reasons lactobacilli are applied in the field of probiotics [15]. It has been documented that lactobacilli produces antimicrobial substances [37] and can interact with intestinal epithelial cells (IECs) and dendritic cells (DCs) preventing the spread of pathogens [41–43], thus providing chemical and physical barriers to enhance innate immunity [15]. More so, they have been found to activate antigen-specific response, thereby improving both innate and adaptive immune responses [29, 41, 44].

Interestingly, different strains of the same species may express different functional properties, for example, lactobacillus alone having over 255 species is a specific example [42, 45, 46]. This suggests that probiotic bacteria are an unlimited source for desirable therapeutic or beneficial properties. Therefore, for their documented probiotic property and particularly their ability to stimulate immunological response, there should be a renewed search for specific strains for functional food development [44, 47, 48] applicable for the prevention and treatment of malaria.

Humoral Immunity to Malaria

Malaria, caused by a protozoan parasite of the genus *Plasmodium*, is a vector-borne disease transmitted by female *Anopheles* mosquitoes during blood feeding. Malaria infected over 218 million people and killed 405,000 in 2018 [49]. This disease is highly prevalent in poor tropical and subtropical areas of the world and is considered the leading cause of illness and death in endemic countries [50, 51]. The clinical presentations resulting from *Plasmodium* infections range from asymptomatic to severe malaria, which is associated with cerebral malaria, severe anemia and respiratory distress [52, 53]. However, the factors that determine malaria severity remain poorly understood, even though the levels of parasitemia are the most regarded determinant [24, 53, 99].

After several exposures to mosquito bites, adult individuals tend to remain asymptomatic which might be due to antibodies developed against the sporozoite, liver-stage, blood-stage, and the sexual-stage *Plasmodium* antigens over time resulting in naturally acquired immunity [52, 54, 55] as evident in asymptomatic infected person [56]. The antibody developed might not affect the malaria parasite directly but can interfere with the *Plasmodium* life cycle at different stages such as blocking the entrance of sporozoite into liver cells, preventing erythrocyte invasion and even limiting transmission in cases of those directed at sexual stage. Further, the immune system plays a vital role in the host by removing parasite at the early stage of infection through cytokines generated and the immune response also regulates the adaptive immunity to prevent excessive production of inflammatory cytokines that are harmful [57–60]. Hence, considering how vital immune response is in the fight against malaria [57, 61], with the increasing rate of drug resistance [62, 63] coupled with low efficacy of pre-existing drugs [64] and vaccine [5], it is important to have a multifaceted approach to stimulating the body natural defense against *Plasmodium* infection and a case for microbiota control can be made (Table 1) [7, 53].

Microbiota-induced Protection Against *Plasmodium*

To curtail the spread of malaria, aside from vector control, transmission-blocking interventions [65–67] are also an area of considerable importance. This has led to the study of the interactions between microbes in the midgut of mosquito revealing the anti-*Plasmodium* effect of mosquito microbiota that reduces the establishment of *Plasmodium* in the mosquito gut, thereby limiting the ability of the vector to transmit the pathogen [68, 69]. Further studies on the gut microbiome of mosquito using different DNA sequencing technologies have identified several midgut-associated bacteria such as *Enterobacter*, *Pseudomonas*, *Chromobacterium*, and *Serratia* that were implicated in preventing *Plasmodium* colonization in vector mosquito [1, 69, 70].

Emphasis had been on mosquito gut because both the parasite and the natural microbiota share this body compartment [71]. Thus, it has been established that bacteria in the midgut do have an inhibitory effect on *Plasmodium*, using mechanisms such as the production of reactive oxygen intermediates with anti-parasitic properties, triggering the innate immune system to produce antimicrobial molecules and also physically preventing the *Plasmodium* from having contact with the mosquito epithelium [70, 71].

Table 1 Summary of different studies on the influence of probiotics and gut microbiota on malaria treatment and prevention

S/N	Microorganisms	Targeted pathogens	Animal models	Key findings/discussion	References
1.	*Escherichia coli* O86:B7	*P. falciparum* 3D7 *P. berghei* ANKA (PbA) *P. yoelii* 17XNL	C57BL/6 α1, 3Gt-deficient mice	Anti α-gal IgM protects human from *P. falciparum* infection Gut pathobiont expressing α-gal prevents transmission of PbA in α1, 3Gt-deficient mice α-gal immunization stimulates the production of Anti α-gal IgM and IgG antibodies that protects against malaria transmission Protective effect of α-gal immunization is enhanced by TLR9 agonist adjuvant Anti α-gal antibodies prevent hepatocyte invasion by PbA sporozoites and have a cytotoxic effect on it as well. Gut microbiota expressing α-glycan might stimulate antibody response that can confer sterile protection to individuals in malaria endemic region	[7, 71, 72, 74, 85, 95]
2.	Gut microbiota	*P. falciparum*	Human study	The composition of gut microbiota from stool analysis indicates the risk potential of infection by *P. falciparum* Population having low risk of malaria has higher proportion of *Lactobacillus*, *Bifidobacterium*, *Streptococcus* in their gut After establishment of *P. falciparum* infection, composition of the gut microbiome has no relationship with the development of febrile malaria	[87]
3.	Lactobacilli	*P. falciparum* *P. yoelii*	Mice, human	Modulation of gut microbiota with probiotic lactobacilli could be helpful in Malaria prevention and treatment	[24, 87]
4.	Gut microbiota	*P. berghei* ANKA (PbA)	BALB/c mice B6 mice	Gut microbiota can be distorted as a result of malaria infection and the extent of alteration to the intestinal microbes can affects the progression to severe malaria in form of cerebral malaria Lactobacilli dysbiosis is associated with severe malaria	[78]
5.	Gut microbiota	*P. yoelii*	C57BL/6 mice	Difference in microbial community determines the extent of resistance to malaria in C57BL/6 N mice	[76]
6.	Gut microbiota	*P. yoelii*	C57BL/6 mice	Mice from different vendor exhibit different parasite burden which might be due to the gut microbiota composition and metabolite produced by gut microbes Immune response in malaria infected host can be shaped by the gut microbiota	[24, 76]

Table 1 (continued)

S/N	Microorganisms	Targeted pathogens	Animal models	Key findings/discussion	References
7.	Lactobacilli	*P. yoelii* *P. yoelii nigeriensis*	C57BL/6 mice C57BL/6 J mice	Mice from different vendors have varying gut microbial composition that affects their resistance to *Plasmodium* infection Type of diet determined the gut microbiome which influences the severity of malaria Difference in gut microbiome influences the susceptibility to malaria Ingestion of lactobacilli alters the gut community and significantly decrease parasite burden Gut microbiota influence the host immunity that determines malaria severity	[24]
8.	Probiotics	*Plasmodium* sp.	NA	Probiotic expressing α-gal maybe linked with toll-like receptors adjuvant in order to stimulate a protective anti- α-gal antibody against malaria Probiotic-based vaccine for malaria transmission blocking	[73, 74, 85]
9.	NA	*P. vivax*	Human Study	Anti-α-gal IgG and IgM could also protect against vivax malaria Relation between anti-α-gal antibodies and parasitaemia does not have significant correlation	[81]
10.	Gut microbiota	*P. berghei*	C57BL/6 mice	Gut microbiota varies during healthy, infected and cured stages in C57BL/6 mice infected with *P. berghei*; highlighting the impact of Malaria infection on gut microbiome	[23]
11.	Faecal microbiota transplantation from malaria resistant mice	*P. chabaudi* AS	Swiss Webster mice	Composition of the gut microbiota affects the parasite burden, maternal morbidity and pregnancy outcome	[25]
12.	Gut microbiota	*P. yoelii* 17XNL	C57BL/6NTac mice	Variation in mice gut microbiota affects the severity of malaria in *Plasmodium yoelii* infected mice	[99]
13.	Mosquito microbiota	*Plasmodium* sp.	NA	Bacterial natural products for the fight against malaria infection focusing on mosquito midgut	[68–70]
14.	Gut microbiota	NA	NA	A case for beneficial microbes for bio-therapeutics is made	[8]
15.	Breast milk microbiota	NA	NA	Improving Infant health by altering the gut microbiota	[93]
16.	Skin, liver and gut microbiota	*Plasmodium* sp.	NA	Host microbiota and their role in *Plasmodium* infection Beyond gut microbiota; lung, liver and skin microbiota play a huge role in *Plasmodium* infection	[53]

Table 1 (continued)

S/N	Microorganisms	Targeted pathogens	Animal models	Key findings/discussion	References
17.	Gut microbiota	*Plasmodium* sp.	NA	The potential of gut microbiota in preventing severe form of malaria	[100]
18.	Fermented maize (omidun, ogi) – lactic acid bacteria	*P. berghei*	Mice	Supports the anti-malaria potential of omidun in malaria treatment	[101]
19.	*Saccharomyces cerevisiae*	*P. falciparum*	Mice	Secretion of Pfs25 and Pfs28 that stimulate malaria transmission-blocking antibodies in mice that can be effective against *P. falciparum*	[102]
20.	Lactobacilli (i.e., *Lactobacillus delbrueckii* subsp. *Bulgaricus*), *Streptococcus thermophilus*	*P. falciparum*	NA	Engineered lactobacilli could be used to express antimalarial peptides, NK2 termed "Antimalaria yoghurt"	[103]
21.	NA	*Plasmodium* sp.	NA	Systematic review on malaria and microbiome reveals gut microbiota affects disease severity and *Plasmodium* infection	[104]
22.	Gut microbiome	*Plasmodium* sp.	NA	Microbial metabolite from gut microbiota could be the molecule influencing the host immunity A case for mucosal immunization for pathogens including malaria is made	[105–107]
23.	Lactobacilli (i.e., *Lactobacillus casei* subsp. *Rhamnosus*)	*P. chabaudi* AS	NIH mice	*L. casei* lowers the level of parasitaemia and affects the viability of *Plasmodium* with increased level of nitric oxide in serum considered as the factor responsible for the increased protection	[108]

Consequently, the inhibitory property exhibited by the midgut commensal bacteria points to the transmission-blocking potential mosquito gut microbiota has on parasitic infection [71]. However, these studies focused on the mosquito midgut microbiota and are limited to the vector and their ability to transmit the parasite to human host [70]. In human, the gut microbiota can regulate the immune system either in blocking transmission (from skin to liver stage) by limiting incidences [65, 72–74] or by upregulating the immune system (Table 2) to reduce the severity of malaria in case of disease establishment (Fig. 1) [24, 25, 75].

Vertebrate Host Microbiota Protects Against *Plasmodium* Infection

Most recent research that delved into the role of probiotics and gut microbiota for the control of parasites has tried to answer the question of how the gut microbiota can be effective in parasite control; however, the exact mechanisms of protection are far from being completely understood [23, 76]. One of the earliest investigations studied the protective role of probiotic lactobacilli (i.e., *Lactobacillus casei* ATCC 7469) in mice infected with *Plasmodium chabaudi* strain AS in which it was observed that parasitemia of infected mice was lower when the mice were treated with the probiotic [77]. It was suggested that the increase in nitric oxide (NO) concentration in the serum of experimentally infected mice fed with *L. casei* was the factor responsible for the increased protection [77]. This submission was based on previous reports on the protective role of NO in severe *falciparum* malaria using S-nitroso-acetyl-penicillamine (SNAP), a NO producer that has an antimalarial effect on *Plasmodium falciparum* by preventing cytoadherence [109], as well as a cytotoxic and cytostatic effect observed in *P. falciparum* asexual stage with a significant effect on the later asexual stage than the trophozoites (ring) stage. The same effect was also observed in *P. chabaudi* AS and *Plasmodium berghei*

Table 2 Immune factors regulated by gut microbiota and their function

S/N	Immunological factors	Function	*Plasmodium* life cycle	References
1.	Anti α-gal IgM and IgG (IgG2b, IgG3)	Binds to *Plasmodium* sporozoite and initiate classical complement pathway thereby inhibiting hepatocyte invasion resulting in the blocking of sporozoite transmission	Skin	[24, 72–74, 80, 85]
2.	$CD8^+$, $CD4^+$, T cells	Initiate sterilizing immunity that is not naturally acquired but relies solely on this adaptive immune factor. They are also antigen specific and target the intracellular stages of infection	Skin and liver	[5, 7, 24, 52, 55, 56, 58, 60, 66, 75]
3.	IFN-γ, TNF, IL-2	Protection against sporozoite and blood-stage antigen. Also, involved in the early stage by inhibiting parasite replication	Liver	[52, 55, 58, 60, 66, 75, 111]
4.	NK, NKT, γδT cells, Macrophages	Stimulate the production of nitric oxide, and nitric oxide synthase that prevent cytoadherence and resetting of infected red blood cells (RBCs) to uninfected RBCs thereby preventing parasite replication	Blood	[52, 56, 60, 106, 108–111]
5.	IL-1β, IL-6, IL-8, IL-12	Pro-inflammatory cytokines that cause fever and severe form of malaria that can be downregulated by gut microbiota	Blood	[17, 52, 58, 60, 90]
6.	TGF-β, IL-10	Anti-inflammatory cytokines (regulatory cytokines) that reduce parasitaemia	Blood	[52, 55, 58, 60, 106, 111]
7.	Treg, DCs	Balancing of the immune system and presents sporozoite to the T cells that help in the activation of B cells for parasite clearance	Blood	[24, 52, 106, 111]

NK natural killer, *NKT* natural killer T cells, *IFN-γ* interferon-gamma, *TNF* tumor necrosis factor, *IL* interleukins, *TGF* transforming growth factor, *DC* dendritic cells

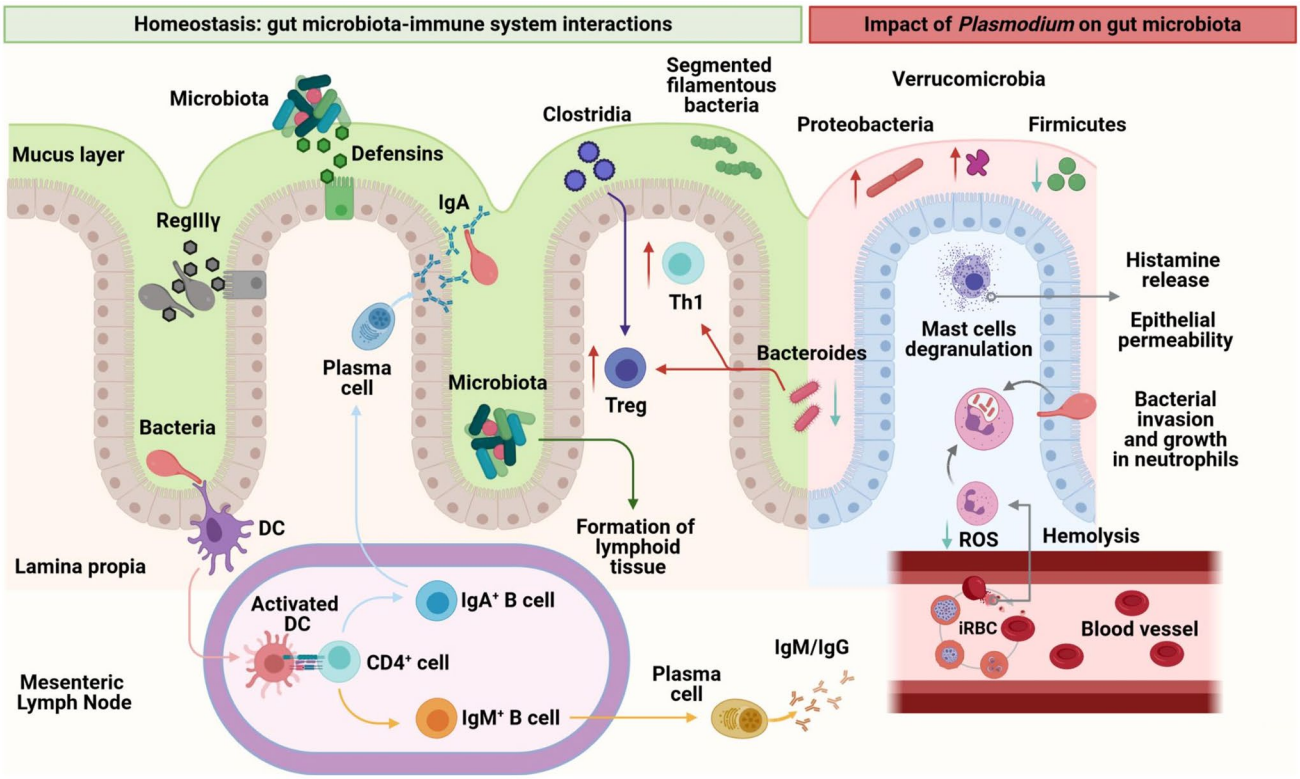

Fig. 1 Disruption of homeostatic gut microbiota-immune system interactions by *Plasmodium* infection. In a healthy status, several immune effectors function together to regulate bacteria-epithelial contacts and maintain gut homeostasis. This includes the mucus layer, epithelial antibacterial proteins (e.g., defensins and RegIIIγ), and IgA secreted by the lamina propria plasma cells. Dendritic cells (DC) recognize bacterial antigens, activate and migrate to lymph nodes where antigen presentation to $CD4^+$ cells occur. Activate $CD4^+$ cells stimulate IgA+ and IgM+ B cells, which in turn differentiate to plasma cells that produce IgA (secreted to the intestinal lumen) and IgM (that enters the blood circulation). Specific members of the microbiota such as Clostridia and Bacteroides stimulate the development and proliferation of Treg and Th1 cells. Malaria promotes the activation and degranulation of mast cells which increases epithelial permeability and bacteria invasion. *Plasmodium* infection of red blood cells (iRBC) also produces hemolysis that by decreasing reactive oxygen species (ROS) production by neutrophils increase the growth of invading bacteria within these polymorphonuclear leukocytes. These changes modulate human microbiota by increasing some taxa such as Proteobacteria and Verrucomicrobia and decreasing other taxa such as Bacteroides and Firmicutes. Figure created with BioRender.com

KSP11 in an animal model, showing an inhibitory effect to the asexual erythrocytic stage [110]. Most importantly is that the effect of NO is more significant in human malaria than rodent malaria. Hence, a probiotic organism that can increase the amount of NO produced in the blood will be a good candidate for modulating the human gut microbiota for malaria treatment (Fig. 2) [77, 108–110]. Furthermore, when C57BL/6 and BALB/c mice were infected with *P. berghei* strain ANKA, it was observed that the degree of malaria severity in terms of cerebral malaria and intestinal pathology varied with the composition of the host gut microbiota [78].

Likewise, Fan et al. [23] reported that lactobacilli were the dominant microbes in healthy C57BL/6 mice infected with *P. berghei* ANKA while in a separate study where C57BL/6 mice were infected with *P. yoelii*, the abundant presence of lactobacilli reduced the severity of malaria observed by the lower parasite burden as compared to naïve mice [24]. Remarkably, in another investigation in which C57BL/6 mice were purchased from a different vendor and infected with *P. yoelii*, the difference in the gut microbiota determined their resistance or susceptibility to malaria [76], thus adding credence to the role of the gut microbiota in malaria severity.

Another microbiota induced protection was observed by Yilmaz et al. [72] in the mouse GalKO model with the knocked-out gene coding for the galactosyltransferase involved in the synthesis of the glycan Gala1-3Galb1-4GlcNAc-R (α-Gal). Mice GalKO were fed with a pathobiont *Escherichia coli* O86:B7 that expresses a high level of α-Gal, a glycan found on the surface of *Plasmodium* sporozoites. The glycan stimulated B cells to produce anti-α-Gal IgM and IgG antibodies that block the transmission of sporozoites from the skin to the liver stage and produces sterilizing immunity in mice. The same effect was derived through immunization with α-Gal antigen [72]. A similar protective effect of anti-α-Gal IgM and IgG was found in

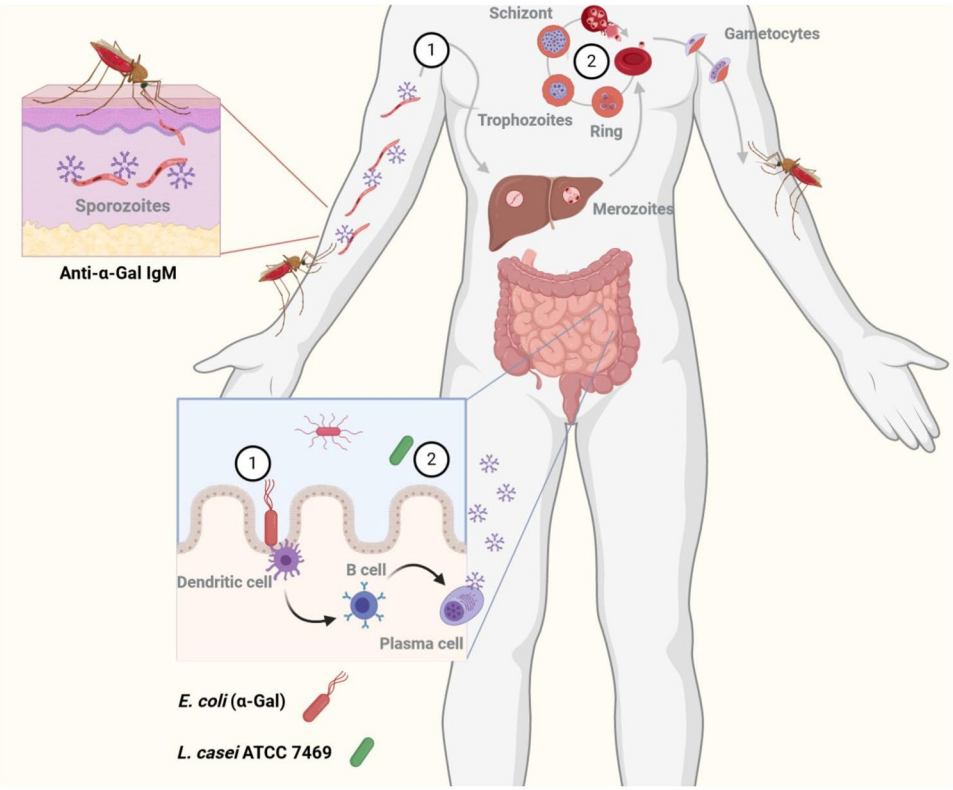

Fig. 2 Elucidating the specific stage of the *Plasmodium* cycle that a probiotic can exert an inhibitory effect. (1) The α-Gal-expressing microbes cause the stimulation of B cells to produce anti-α-gal IgM and IgG. The α-gal glycan sequence is similar to the one present on *Plasmodium* sporozoite surface; thus, anti-α-gal antibody generated has been reported to bring about sterile immunity by blocking the transmission of *Plasmodium* sporozoite from skin to liver stage through complement-mediated lysis of sporozoites in the skin. (2) *Lactobacillus casei* ATCC 7469, a probiotic, has been studied to bring about reduced level of parasitaemia and lowers the viability of *Plasmodium* by increasing the serum concentration of nitric oxide affecting the erythrocytic stage. Abbreviation: α-Gal, galactose-α-1,3-galactose. Figure created with BioRender.com

human exposed to *Plasmodium*-infected mosquito [72, 79]. Humans have evolutionarily lost the ability to synthesize α-Gal resulting in the immune system releasing antibodies specific to this carbohydrate [80–82]. It has been reported that all non-immunocompromised persons have the ability to produce antibodies against α-Gal [83], which makes up approximately 1% of IgG and 5% of IgM circulating immunoglobulins [84]. Thus, the amounts of anti-α-Gal IgM/IgG observed in non-infected individuals and those living in malaria-endemic areas such as Mali and Senegal are protecting them from malaria parasite [72, 79, 81]. Hence, populating the gut with probiotics that expresses α-Gal on their cell surface might be effective in stifling the transmission rate by boosting the anti-α-Gal immune response mediating the lower incidences of malaria (Fig. 2) [7, 71, 74, 85]. At the same time, α-Gal has been proposed for vaccine development to target *Plasmodium* parasites at different stages [56, 65, 74, 85, 86].

However, the most compelling argument for the role of microbiota in malaria parasite infection in humans is from the study of Yooseph et al. [87] that investigated the relationship between the gut microbiota composition and *P. falciparum* infection in malaria-endemic areas. It was observed from the analysis of stool microbiota that the presence of a higher number of *Streptococcus* and *Bifidobacterium* correlates with a lower risk of *P. falciparum* infection although without a relationship with febrile malaria [87].

Consequently, the use of probiotics for functional food development as a dietary supplement would be a good strategy for more investigation in order to find ways to prevent malaria incidence and also reduce the severity in case of infection [73, 74].

Developing Functional Foods to Stimulate Anti-α-gal Immune Response, the Search Continues

Ellie Metchnikoff, a Russian scientist, came up with the hypothesis that some microorganisms are beneficial and improve human health by observing the Bulgarians that consume fermented milk in large quantities, which he assumed as the sole factor for their long life and good health [17, 88, 89]. This hypothesis was termed as "theory of longevity" as he observed the effect that these bacteria in the human intestine have on general well-being, thus serving as an upshot for further study that investigated the preventive role of the gut microbiota in diseases [90, 91]. Later on, Lilly and Stillwell used the term probiotics signifying "prolife" [31, 42], a term that has undergone several definitions but currently is defined as viable, non-pathogenic microorganisms that, when ingested in adequate amounts, are able to reach and establish in the gut to confer health benefits to the host [44].

Furthermore, in the works of Maegraith et al. [92] in which different groups of rats and mice were infected with *P. berghei* to induce blood-stage malaria and were fed with a normal diet, cow milk, reconstituted Oster milk, and reconstituted Australian dried milk, it was observed that as opposed to the normal diet, the milk diet contains some dietary factors that suppressed the development of *Plasmodium* as prevention of death was observed in some of the treated animals. It was concluded that some attention should be paid to the effect of milk in human malaria as breastfed children rarely have severe malaria while acknowledging that at the same period, another researcher opined that there is a factor in milk that has a protective role against some viral infections [92, 93].

Subsequently, in the last decade, there is a renewed interest in what this factor could be. At first, Lokki et al. [94] suggested that lactase persistence gene could be responsible for the increasing resistance to malaria among the Fulani tribe of West Africa but could not establish a statistical significance with it. Nevertheless, from the study, they considered that since the Fulani feed a lot on milk product, there must be a factor in milk that is responsible for the observed resistance. Hence, the study maintained that the nutrient element in milk, immunomodulating components, and milk-induced para-aminobenzoic acid (PABA) deficiency might be the reason for the protection against malaria [94].

However, Maegraith et al. [92] and Lokki et al. [94] did not consider the role of microbes in their study [93], a factor that Yilmaz et al. [72] considered when *E. coli* O86:B7 effect on malaria severity was studied. The bacteria enabled immune protection against malaria infections in the experimental mice, establishing a possible human gut microbiota-driven immunity against malaria by limiting infection incidence [71]. Considering that *E. coli* O86:B7 is not naturally associated with foods and the pathogenic strains of the specie exist, it is not overtly suitable as a candidate for probiotics [73].

Thereafter, lactobacilli with documented probiotics properties were used to formulate yoghurt that was fed to experimental mice infected with *Plasmodium*, resulting in an antecedent decrease in parasite burden [24]. Besides, when cecal content of malaria resistant mice was transplanted to susceptible mice, they developed resistance to severe malaria and the afterwards genomic analysis of the gut microbiota revealed the abundant presence of lactobacilli establishing the role of the microbiota in the severity of malaria [24, 25, 76, 99]. Moreover, in comparison between the works of Maegraith et al. [92] and Villarino et al. [24] despite the difference in the research timeline, it can be concluded that the answer to the unknown factor in milk that suppresses the development of *Plasmodium* has to do with the milk microbiota [93]. Additionally, the transplantation of fecal microbiota that confers malaria resistance to pregnant mice that resulted in lower parasite burden prevented malaria anemia and enhanced the pregnancy outcome support the importance of gut microbiota composition in malaria severity [25].

Considering the established beneficial effect of the gut microbiota as it relates to human health (Table 1), particularly to malaria prevention and treatment, there is need to bio prospect for lactobacilli with the needed property that can be developed as a functional food. A functional food containing probiotic organisms that can protect against parasite transmission and/or reduce the severity by stimulating immune response (Table 2) will be desirable for modulating the gut microbiota [40, 53, 91, 95–98].

The understanding of how gut microbiota exerts a positive effect on *Plasmodium* infection is still not clear, and all shreds of evidence are mainly from an animal model using rodent-malaria studies. It is also worthy of note that the gut community of mice differ considerably from humans as well as between mice having different diets and breeding environment [23–25, 99]. Notwithstanding, the few human studies on the correlation between gut microbiota composition and malaria severity is a pointer to the fact that the modulation of the gut microbiota with probiotics or functional food could be an alternate means in malaria management (Table 1). As the case of resistance to antimalarial keeps growing coupled with the fact that vaccine development is still at the early stage, future research can focus on how modulation of the gut microbiota can aide vaccination for the stimulation of specific immune response against malaria.

Concluding Remarks and Future Perspectives

Gut microbiota has a great impact in modulating immune response [24, 76], implicated in parasite clearance [25, 76, 77] and a potential tool for vaccine development [74, 85, 105–107]. Considering all evidence from the role of gut microbiota in malaria severity, the time is ripe for an intensified study on probiotics for the control of malaria and prevention of its severe form in which development of functional food is vital. The findings that have supported the impact of gut microbiota with respect to their protective role in malaria pathogenesis need to be scaled up for its intended benefits. Development of functional food containing probiotics from fermented foods with desired properties or genetically modified bacterial strains for the purpose of manipulating the gut microbiota is important to advance the control of malaria and other infectious diseases.

Despite the advances and potential impact that vaccines represent for the prevention and control of infectious diseases, interventions boosting the immune response to α-Gal with a broader and not pathogen-specific immunity may contribute not only to the control of malaria but also

to other diseases. Probiotic-based formulations with abundant commensal bacteria of the gut and lung microbiota with high α-Gal content may be developed for the prevention and control of malaria and other major infectious diseases affecting humans worldwide (Fig. 2). One of the major challenges of vaccination campaigns in poor regions with a high prevalence of infectious diseases is the distribution and administration of the vaccine. The possibility of developing probiotics that can be delivered in stable formulations such as a yoghurt or food supplements will make these interventions easier to distribute and administer. These formulations have a low production cost and are easy to administer with a major impact in regions with limited access to health services.

Future research should address the mechanisms mediated by α-Gal immunization; the characterization of gut and lung microbiota including α-Gal content in infected, exposed, and healthy individuals; and the identification of commensal bacteria with α-Gal modifications for the development and evaluation of probiotic-based formulations. Even though the mechanism of action is still a study in process, the usage of probiotics to stimulate immune system towards malaria disease holds a significant prospect. Thus, there should also be increase interest in clinical study beyond field observation while more funding should be made available for meticulous study of fermented foods and formulation of functional foods for the same purpose.

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Declarations

Conflict of Interest The authors declare no competing interests.

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