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Gastrointestinal worms and bacteria: From association to intervention

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Abstract

A plethora of studies, both experimental and epidemiological, have indicated the occurrence of associations between infections by gastrointestinal (GI) helminths and the composition and function of the host gut microbiota. Given the worldwide risk and spread of anthelmintic resistance, particularly for GI parasites of livestock, a better understanding of the mechanisms underpinning the relationships between GI helminths and the gut microbiome, and between the latter and host health, may assist the development of novel microbiome-targeting and other bacteria-based strategies for parasite control. In this article, we review current and prospective methods to manipulate the host gut microbiome, and/or to exploit the immune stimulatory and modulatory properties of gut bacteria (and their products) to counteract the negative impact of GI worm infections; we also discuss the potential applications of these intervention strategies in programmes aimed to aid the fight against helminth diseases of humans and livestock.

KEYWORDS
bacterial extracellular vesicles, bacterial vaccines, bioactive bacterial metabolites, helminth–gut microbiota interactions, postbiotics, prebiotics, probiotics

1 | INTRODUCTION

Gastrointestinal (GI) helminths of humans and animals are amongst the most prevalent pathogens globally, causing significant morbidity and mortality particularly in developing areas of the world. According to the World Health Organisation, 24% of the global population is currently infected by GI helminths, including roundworms (e.g., *Ascaris lumbricoides*), whipworms (e.g., *Trichuris trichiura*) and hookworms (e.g., *Necator americanus*).[1] Clinical manifestations of human GI helminth infections include anaemia, iron and protein deficiency, nutrient malabsorption, and growth and cognitive impairment, resulting in >5 million disability-adjusted life years.[1–3] Similarly, GI helminths of veterinary significance, such as the 'barber's pole worm' *Haemonchus contortus*, the 'brown stomach worm' *Teladorsagia circumcincta* and the 'thread-necked worm' *Nematodirus battus*, represent a substantial burden on the global livestock industry, due to significant reductions in animal weight gain, wool and milk production, and carcass quality.[4] Strategies aimed to mitigate losses associated with GI helminth infections in both humans and animals have largely relied on chemotherapeutic interventions, namely the administration of anthelmintics.[5] However, over the past several decades, anthelmintic overexposure and misuse have led to the emergence of drug resistant strains of numerous helminth species of veterinary importance, thus hindering our ability to effectively control helminth infections in livestock and raising concerns that similar mechanisms might emerge in GI helminths of humans.[6] Global research efforts have long been focused on the development of alternative methods of helminth control, including anti-helminth vaccines (reviewed by Claerebout and

Geldhof[7]). Nevertheless, despite some successes (i.e., Dictol™ and Barbervax™, which provide protection against the bovine lungworm, *Dictyocaulus viviparus*, and *H. contortus*, respectively[8]), current anti-helminth vaccine data are often characterized by varying efficacy, thus suggesting that other immunity-independent, unexplored factors may contribute, at least in part, to helminth establishment and survival within the vertebrate host.[9–12]

Over the past decade, increasing evidence has supported the hypothesis that the host gut microbiome may represent a key player in host–parasite relationships. This hypothesis has largely stemmed from the observation that GI helminth infections are associated with profound alterations in host gut microbiota composition and function, both in humans[13,14] and animals, including livestock.[9,15–17] Whilst the biological significance of such alterations is yet to be fully elucidated, possible roles in infection establishment, modulation of host immune responses, and prevention of parasite expulsion have been postulated.[18–20] For this reason, a number of studies have speculated that microbiome-targeting and other bacteria-based interventions may pave the way to the discovery of alternative strategies of parasite control. In this article, we discuss current techniques of gut microbiota manipulation, e.g., via the administration of probiotics, prebiotics and nutritional supplements, and review prospects for the application of novel microbiome-targeting methods, probiotic-based vaccines and gut-bacteria-derived products to the development of new sustainable approaches for GI helminth control in humans and livestock.

2 | CURRENT MICROBIOME-TARGETING STRATEGIES FOR HELMINTH CONTROL

Microbiome-targeting therapeutics have been administered as adjuvants to primary treatment protocols with the aim of ameliorating symptoms caused by a range of infectious and non-infectious diseases, including, for instance, ulcerative colitis and *Clostridium difficile* infection.[21,22] Such strategies aim at (re)shaping gut microbial communities, for instance, through the administration of (i) bioactive dietary components (e.g., prebiotics) or (ii) non-resident bacteria, including probiotics, bespoke bacterial consortia and faecal bacterial communities obtained from healthy donors.[22-27] However, efficacy is often highly variable[18,28-30] and a thorough understanding of the events that follow these interventions and mediate health-promoting effects is needed in order to fully exploit the potential benefits of microbiota manipulation strategies.[22-27] Whilst limitations in current knowledge of such mechanisms have largely hindered large-scale applications of diet supplementation and bacterial transfer to the management of helminth infections, several studies have investigated the efficacy of microbiome-targeting therapeutics—namely, pre- and probiotics—as means of controlling GI helminthiases of humans and farmed animals.

2.1 | Prebiotics and nutritional supplements

Dietary interventions based on the administration of prebiotics have long been regarded as promising tools to boost immune function and resilience against helminth infections, due to the substantial impact that diet exerts on gut microbiota composition and function.[27,31] Prebiotics are defined as 'non-digested food components that, through the stimulation of growth and/or activity of a single type or a limited amount of microorganisms residing in the gastrointestinal tract, improve the health condition of a host'[25,26] (Figure 1A). Several studies have investigated the efficacy of prebiotics (e.g., inulin and tannins) coupled with, or in alternative to anthelmintic treatment, to combat helminth infections in farmed animals (reviewed by Cortés et al.[8]). Prebiotic inulin is fermented by gut bacteria into short-chain fatty acids (SCFAs), that is, products of colonic bacterial metabolism known to play crucial roles in the maintenance of mucosal integrity and immune homeostasis.[32] In a rodent model of metabolic disease, inulin consumption was related to increased gut microbial alpha diversity, improved intestinal barrier function and reduced inflammation.[33] In pigs, dietary supplementation with inulin resulted in significantly lower worm burdens and/or reduced female fecundity of the large intestinal nematodes *Trichuris suis* and *Oesophagostomum dentatum*, respectively, thus indicating that this prebiotic might exert helminth-eradicating effects.[34,35] In a recent study, Myhill et al.[36] speculated that inulin might act synergistically with *T. suis* to promote local Th2 polarization and colonic mucosal integrity; in the same study, increases in faecal populations of beneficial *Lactobacillus* and *Bifidobacterium*, and simultaneous reductions of pro-inflammatory *Proteobacteria* and *Firmicutes* were observed in inulin-fed animals.

Tannins are bioactive secondary polyphenolic metabolites derived from a variety of natural sources, including wood and bark, that display strong antimicrobial activity, for example, against pathogenic bacteria of the genera *Escherichia*, *Shigella*, *Salmonella* and *Pseudomonas*, amongst others.[37] In the large intestine, undigested tannins may promote the growth of beneficial bacteria and serve as substrates for SCFA production.[38] Tannin-rich plants and supplements have long been regarded as active against several GI nematodes of livestock, such as *H. contortus*, *T. circumcincta*, *Ostertagia ostertagi*, *Trichostrongylus colubriformis* and *Ascaris suum*.[39–42] In addition, tannins may contribute to the elimination of GI helminth infections in ruminants via indirect mechanisms that involve the formation of tannin–protein complexes that render the latter unavailable to ruminal bacteria. By reducing ruminal degradation of proteins, dietary tannins indirectly lead to increased levels of usable proteins, and thus, of absorbable amino acids and peptides in the small intestine that, in turn, may enhance anti-parasite mucosal immunity.[43]

In a recent study, administration of tannin-rich products (condensed tannin from *Acacia mearnsii*) to lambs experimentally co-infected with *H. contortus* and *T. colubriformis* resulted in ~50% decrease in mean faecal egg counts, albeit statistical significance was not reached.[44] Moreover, experimental helminth infection along with tannin supplementation resulted in significant alterations of the composition and predicted function of the ovine ruminal microbiota, which included the expansion of populations of *Lactobacillus* and *Bifidobacterium* and over-representation of bacterial genes involved in nitrogen metabolism. In non-infected control lambs, tannin supplementation was linked to a significant increase in total ruminal SCFAs, and particularly of acetate, butyrate, valerate and isovalerate. No

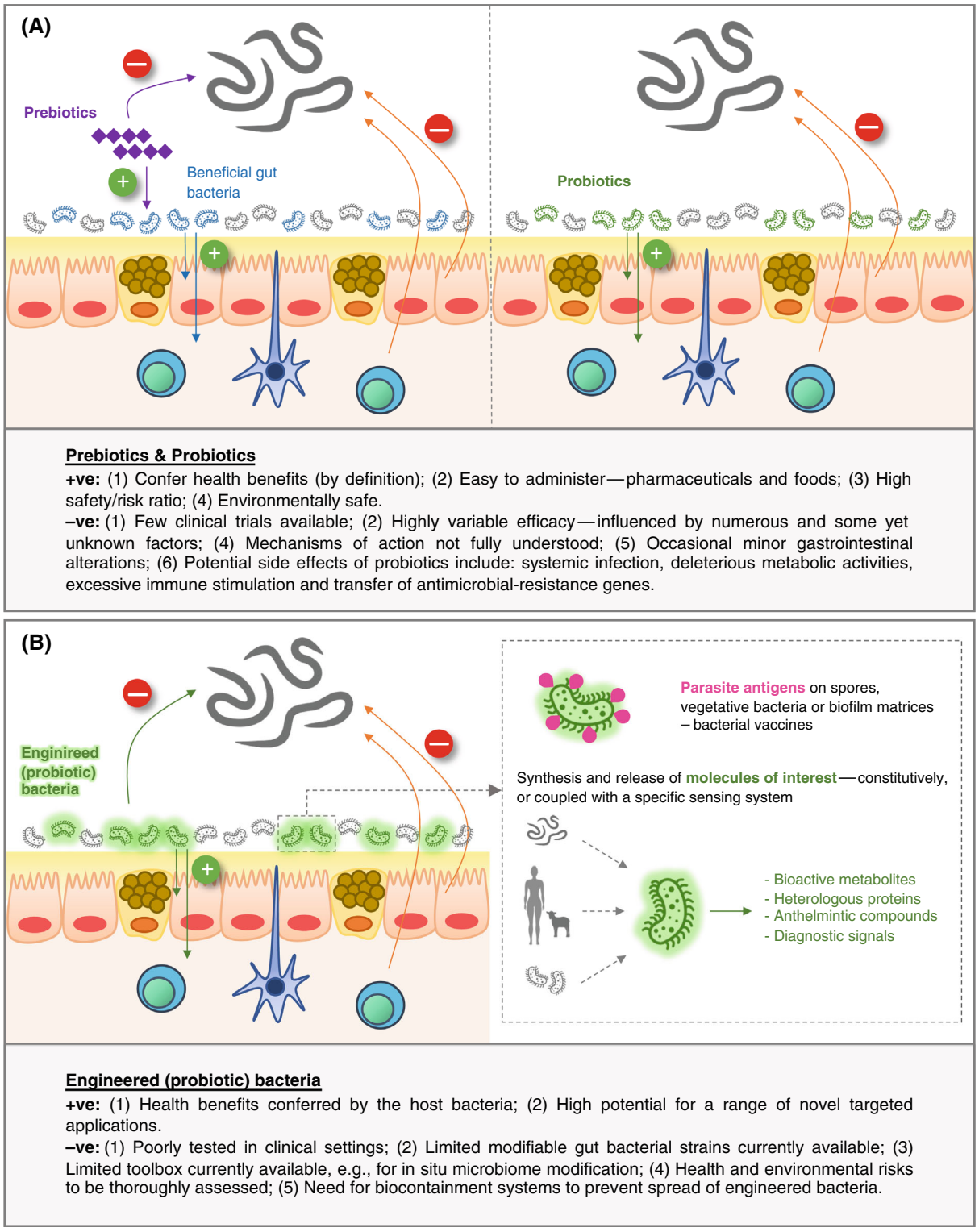

FIGURE 1 Schematic representation of the general mode of action of prebiotics and probiotics (A) and bioengineered (probiotic) bacteria (B) against gastrointestinal (GI) helminths. Briefly, both prebiotics and probiotics can improve the host response towards GI helminths through different mechanisms, including enhanced gut barrier function, unspecific immune stimulation and/or modulation, and luminal pH change, amongst others. Whilst such beneficial properties are inherent to probiotic bacteria, prebiotics stimulate changes in the GI environment by promoting the expansion of gut beneficial bacteria, either directly or indirectly, i.e., through cross-feeding mechanisms. Furthermore, some prebiotics (e.g., tannins) are thought to exert direct anthelmintic effects. The main positive and negative aspects currently associated with each microbiome-targeting or bacteria-based intervention strategy are summarized directly under each panel.[58,109,110]

significant differences were detected in SCFA concentrations between supplemented and non-supplemented infected lambs. Nonetheless, the percentage of ruminal butyrate was lower in the latter group when compared to the former, and coincided with reduced proportions of butyrate-producing bacteria (e.g., families *Lachnospiraceae* and *Ruminococcaceae*, and genus *Butyrivibrio*) and underrepresentation of butyrate-related metabolic pathways.[44] Whilst these results point towards an impact of dietary tannins on host–parasite–gut microbiota interplay, whether such alterations in gut microbiota composition and function exert a protective effect against helminth infection and/or pathology is yet to be experimentally demonstrated.

Other polyphenol-rich vegetal products have been reported to interfere with gut bacterial metabolism and mucosal immunity during GI nematode infections. Amongst these, diet-administered grape pomace was associated with enhanced recruitment of eosinophils and mast cells to the small intestinal mucosa of pigs infected with *A. suum*.[45] In the same study, such a polyphenol-enriched diet was associated with significant changes of the gut microbial composition of helminth-uninfected animals, unlike that of *A. suum*-colonized pigs. Nevertheless, grape pomace supplementation was linked to increased colonic concentrations of the SCFA propanoate, in both *A. suum*-infected and -uninfected pigs.[45] Altogether, data from these studies lend credit to the hypothesis that prebiotics and other nutritional supplements may contribute to alterations in the abundance and/or metabolic function(s) of selected gut bacteria that, in turn, exert beneficial effects to host health during GI helminth infections. However, the mechanism(s) via which dietary products modulate the host gut microbiome, as well as the implications of such changes for helminth–microbiota–host immunity interactions remain largely unexplored.

Of note, establishing whether the effects of microbiota-targeting nutritional interventions on host–helminth interactions are consistent across host–parasite pairs will be key to progress towards 'real-world' applications of such strategies. Indeed, the downstream consequences of helminth colonization on host gut microbial communities are characterized by substantial variations[46] and, thus, it seems plausible that these inconsistencies may extend to the effects of dietary interventions on host–parasite–microbiome interactions. Reinforcing this concern, and in contrast to the abovementioned benefits of inulin supplementation on swine infections by *T. suis*, administration of this prebiotic to mice resulted in reduced *Trichuris muris* expulsion, an outcome that was linked to the development of a potent Th1-skewed immune response accompanied by gut microbial dysbiosis.[47] Taken together, these discrepancies highlight the need for caution not only when evaluating the applicability of dietary interventions for the control of helminth infections across animal species, but also for potential translational studies from animal models to humans. Indeed, whilst bidirectional links between human nutritional status and parasite infections—as well as between diet and gut microbiota composition and function—have been established, thus far no information is available on the impact that dietary interventions may exert on human helminth infections.[48] Several host- and parasite-related factors, as well as additional external variables, can contribute to the substantial variability of findings arising from helminth–microbiome interaction studies in humans.[49] Nevertheless, standardized epidemiological studies exploring the impact of dietary interventions and other microbiota manipulation strategies (e.g., probiotics) on (i) infection burdens, (ii) nutritional and morbidity indicators, and (iii) the gut bacterial composition and metabolic potential of individuals from helminth-endemic areas will lay the necessary basis for the development of microbiome-targeting tools to combat diseases caused by human helminths.

2.2 | Probiotics

Probiotics are live, non-pathogenic microorganisms that confer health benefits when delivered in adequate amounts (reviewed by Saracino et al.[23]) (Figure 1A). In humans, probiotics are often administered to assist the amelioration of symptoms of chronic inflammatory conditions, such as inflammatory bowel disease, atopic dermatitis or allergy; in ruminants, probiotics are thought to improve feed efficiency—for example, by enhancing nutrient absorption—and limit the onset of metabolic diseases.[23,24] Probiotics span a range of bacterial genera, and their functions include modulation of host immune responses, competition with pathogenic microorganisms (for both space and nutrients), and inhibition of bacterial toxin production. A myriad of mechanisms underpin these functions, and multiple modes of action through which probiotics may promote GI homeostasis and host health have been reported.[25,50]

Several studies have attempted to identify and characterize species of probiotics capable of eliciting protection against GI helminth infections, and these are reviewed elsewhere.[23,51] Instead, our focus centres on considerations regarding the current status and future perspectives of the application of probiotics to the control and/or management of GI helminthiases in humans and species of veterinary interest.

Administration of probiotic strains of the genera *Lactobacillus*, *Lactiplantobacillus*, *Bacillus* and/or *Enterococcus* has led to significant enhancement of host immunity against, and/or of reduced burdens of, *Trichuris*, *Trichinella* and *Toxocara*, as well as of blood flukes of the genus *Schistosoma*.[23,51] It is worth noting, however, that the majority of these studies were conducted in murine models of infection, and thus, administration of such probiotics to worm-infected humans and animal species of veterinary interest in 'real-world' scenarios might result in different outcomes. For instance, a 58% and 70% reduction in burdens of *Trichinella spiralis* adult worms and muscle larvae, respectively, was observed in mice supplemented with *Lactobacillus casei* ATCC 7469.[52] Whilst data from this study are promising, further experiments are needed to unequivocally assess the protective effects of *L. casei*, as well as other probiotic bacteria, on *T. spiralis* infection in other host species. Indeed, studies conducted in helminth-infection models using large mammals (i.e., pigs) have shown a limited effect of the administration of dietary probiotics against infection.[53,54] Administration of several probiotics (i.e., *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* subspecies *animalis*) to pigs experimentally infected with *A. suum* failed to reduce the number of fourth-stage larvae in the intestine of colonized animals, although altered gene expression levels

of cytokines and innate immune receptors were reported in the bronchus- and/or gut-associated lymphoid tissue (GALT).[53,54]

Other studies have reported that the administration of probiotics may favour the establishment of helminth infections. For instance, exposure of mice to *L. casei* and *Lactobacillus taiwanensis* BL263 prior to infection with *T. muris* and *Heligmosomoides polygyrus*, respectively, was followed by changes in host immunity that resulted in higher worm burdens.[29,55] In particular, administration of *L. taiwanensis* prior to *H. polygyrus* infection was accompanied by elevated frequencies of regulatory T cells (Treg) in the GALT that, in turn, promoted worm survival.[55] Similarly, exposure to *L. casei* prior to *T. muris* infection was associated with a reduced production of Th1- and Th2-related cytokines in mesenteric lymph nodes and Peyer's patches; whilst this observation is compatible with activation of Treg-mediated immune responses, these were not specifically assessed.[29]

Taken together, the evidence summarized above suggests that bacterial probiotics are associated with substantial alterations of the host GI environment that might, directly and/or indirectly, influence the establishment and survival of invading helminths. Such effects are likely to be highly dependent on the host–parasite pair under consideration. Furthermore, given the substantial inter-individual variability observed in several of these experiments, the application of probiotics as a universal strategy to improve host health during helminth infections appears unlikely. Nonetheless, defining the mechanisms through which probiotics modulate host immunity and/or helminth colonization and survival will pave the way towards future strategies aimed at triggering specific health-promoting effects, for example, via the administration of immunologically active bacteria-derived products.

3 | GENETIC ENGINEERING AND SYNTHETIC BIOLOGY: OPPORTUNITIES FOR FUTURE MICROBIAL-BASED STRATEGIES AGAINST HELMINTH INFECTIONS

Synthetic biology consists in the application of genetic engineering principles (i.e., manipulation and modification of the genetic material of an organism) and DNA assembly methods to redesign the genome of existing organisms in order to achieve practical benefits of interest to a range of scientific and technological fields, such as biomedicine, food industry or agriculture.[56,57] Modification (as well as modulation) of microbial cell function and/or behaviour can be achieved using several genetic engineering tools and strategies, that may be applied to transform both resident gut bacteria, as well as non-resident probiotic species, with the ultimate goal of exerting a positive effect on host health (reviewed by Bober et al.[58]; Figure 1B). Nevertheless, to date, bacterial genetic engineering can reliably be applied to a relatively narrow group of culturable gut colonizers, including several lactic acid bacteria, bifidobacteria and members of the genus *Bacteroides*. Moreover, since genetic modification of bacterial strains is performed *in vitro*, similarly to live exogenous bacteria (e.g., probiotics), the success of interventions based on the administration of engineered bacteria is strictly dependent on the ability of the latter to stably colonize the host gut and to carry out their function(s) at a level sufficient to induce the desired beneficial effects.[58] In an attempt to overcome these limitations, increasing research efforts are being directed towards the development of novel synthetic biology tools that enable efficient, stable and safe editing of the gut microbiome *in situ*.[58,59] In this section, we review current trends in the use of bioengineered bacteria to the management and/or control of helminth infections, and briefly discuss potential future applications of such technologies in this field.

3.1 | Vaccination against GI helminths using engineered probiotics

GI bacteria communicate with the mammalian immune system through an extensive network of interactions that determine training and development of both innate and adaptive immunity, and contribute to the maintenance of immune homeostasis and overall host health. For instance, microbiota-derived pattern recognition receptor ligands and selected metabolites interact directly with enterocytes and gut immune cells to regulate inflammatory responses and/or promote gut barrier function; moreover, these molecules can reach the bloodstream and modulate immunity in organs and tissues physically distant from the GI system (reviewed by Zheng et al.[60]).

Anti-helminth control strategies may take advantage of the close interplay between GI bacteria and the host immune system. One example is oral live vaccines, that consist of probiotic bacteria modified to enable the synthesis of heterologous antigens (e.g.,[61]). For instance, spores obtained from *Bacillus subtilis* strains have been engineered to display parasite antigens on their surface and used to stimulate specific immune responses against *Schistosoma japonicum* (in mice[62]), *Clonorchis sinensis* (in mice[63]), *Opisthorchis viverrini* (in hamsters[64]) and *H. contortus* (in sheep[65]). Once repeatedly ingested, engineered *B. subtilis* spores induced specific humoral responses against parasite antigens, both locally and systemically. In particular, specific serum IgG and gut mucosal and/or biliary IgA were elevated in rodents immunized with *B. subtilis* spores expressing *S. japonicum*, *C. sinensis* and *O. viverrini* antigens—namely glutathione-S-transferase, a cysteine protease and an extracellular-vesicle-derived tetraspanin, respectively.[62-64] Remarkably, in the latter study, enhanced antibody responses in vaccinated hamsters were linked to a significant impairment in worm growth and a >50% reduction in both adult flukes and faecal egg outputs, compared to non-immunized animals.[64] Similarly, repeated oral immunization of sheep with *B. subtilis* spores expressing GADPH from *H. contortus* resulted in significant reductions in faecal egg counts post-challenge infection, as well as in the total number of adult worms recovered at post-mortem. Such decrease in parasite burdens was associated with reduced abomasal damage and improved weight gain, and linked to an enhanced proliferation capacity of peripheral blood mononuclear cells, as well as elevated titres of anti-GADPH antibodies in serum and intestinal mucus (IgG and IgA, respectively). In addition, expanded populations of *Lactobacillales*, a group of bacteria with known probiotic functions, were observed in the abomasal microbiota of vaccinated animals.[65]

Bioengineered spores from *B. subtilis* have also been tested for immunization of dogs against the tapeworm *Echinococcus granulosus*.[66] In this study, ingested recombinant *B. subtilis* spores successfully germinated in the host gut, resulting in vegetative, biofilm-forming cells that exposed parasite antigens (i.e., paramyosin and tropomyosin) on the surface of the extracellular matrix. Whilst orally immunized dogs developed specific IgG responses against *E. granulosus* antigens, no worm expulsion and/or challenge experiments were performed.[66]

Similar approaches have been applied to vaccination studies in murine models of *T. spiralis* infection. In particular, oral immunization with recombinant *Lactobacillus plantarum* strains expressing *Trichinella* antigens led to substantial reductions in burdens of intestinal adult worms and larvae encysted in skeletal muscle; both these outcomes were linked to enhanced specific antibody responses and increased production of IFN-γ, IL-4 and IL-17 in the GALT and/or spleen of immunized animals.[67,68] Moreover, repeated administration of *L. plantarum* engineered to produce mouse IL-4 was demonstrated to elicit type 2 immune responses against challenge infection, leading to substantial reductions in parasite burdens in both the small intestine and skeletal muscle.[69]

An alternative immunization strategy against *T. spiralis* consisted in the administration of recombinant *L. plantarum* expressing fibronectin-binding protein A from *Staphylococcus aureus* that confers lactobacilli the ability to effectively invade mammalian cells.[70-72] Invasive lactobacilli transformed with eukaryotic expression plasmids act as live bacterial vectors of exogenous DNA directly into host cells.[70] Repeated oral immunization with transformed invasive *L. plantarum* coding for *T. spiralis* antigens—either alone or in combination with mouse IL-4—conferred partial protection against challenge *Trichinella* infection and resulted in reduced burdens of both adult worms and larvae. These protective effects were linked to enhanced local (IgA) and systemic (IgG) antibody responses against *T. spiralis* antigens, as well as increased production of Th1 and Th2 cytokines in the mesenteric lymph nodes and spleen of immunized mice post-challenge infection.[71,72] Whilst, in both studies, vaccination with eukaryotic vectors coding for both *T. spiralis* antigens and mouse IL-4 was associated with the highest level of protection against infection, adult worm and larval burdens were significantly lower in mice treated with control invasive *L. plantarum* (i.e., transformed with empty vectors) compared to bacteria-unexposed mice. This observation suggests that the bacterial vector alone might assist the development of effective immune responses against *T. spiralis*.[71,72]

3.2 | Perspectives for additional uses of bioengineered bacteria in the fight against GI helminths

Beside stimulating and/or modulating host immunity, gut-associated and probiotic bacteria may be bioengineered for additional purposes, such as combating pathogens, diagnosing diseases or modifying host metabolism.[58] These applications are yet to be thoroughly explored in the field of helminth infections; nonetheless, emerging evidence in other areas of health science suggests that they might become viable alternative strategies in the battle against GI helminths of humans and animals.

Synthetic biology has been applied to the construction of gut bacterial strains that are able to sense and respond to intestinal pathogens. For instance, *Lactococcus lactis* was genetically programmed to detect a sex pheromone from the opportunistic pathogen *Enterococcus fecalis*, and respond by secreting anti-enterococcal bacteriocins that impaired *E. fecalis* growth and viability in bacterial co-cultures.[73] Similarly, *L. lactis* strains were engineered to constitutively express and secrete bioactive *Bacillus thuringiensis* crystal protein 5B (Cry5B).[74] Cry5B from *B. thuringiensis* binds to the gut of both free-living and parasitic nematodes via a worm-specific glycolipid receptor; this selective binding damages the worm gut and induces parasite death without side effects for the host.[75] Cell lysates from Cry5B-producing *L. lactis* were highly toxic for the free-living nematode *Caenorhabditis elegans*, thus paving the way to the use of engineered bacteria as oral anthelmintic agents.[74] More recently, it has been speculated that existing compositional differences between helminth- and host-associated microbiota may be exploited to deliver drug-producing synthetic bacteria directly into the worm gut.[76]

Bacteria-mediated drug delivery might also be optimized by taking advantage of bacterial biosensors able to detect and respond to specific environmental cues.[58] Indeed, several bacterial species have been engineered to deliver a range of biomolecules with therapeutic activity, either continuously or upon sensing a particular stimulus, and some of these are already being evaluated in pre-clinical and clinical trials.[58,77] The gut of parasitized hosts harbours a vast array of helminth-derived small molecules (i.e., chemical compounds whose molecular weight is <1 kDa) that, potentially, could represent targets of bacterial biosensors for *in situ* detection of GI helminths.[78] Nevertheless, in order for this technology to be fully exploited, two key technical barriers must be overcome; first, specific molecules acting as unequivocal indicators of infection must be identified; second, these indicators must be detectable through bacterial biosensors. Once these live biosensors are developed, their use could be extended to diagnostic purposes,[78,79] coupling the detection system with a response mechanism that outputs a detectable (and measurable) signal.[80]

Lastly, microbial bioengineering approaches might also be applied to fine-tuning of host–parasite interactions to achieve a beneficial effect for the host. For instance, genetic manipulation of aromatic amino acid metabolism in the gut commensal *Clostridium sporogenes* resulted in altered serum levels of tryptophan-derived metabolites in mice, and led to significant changes in peripheral blood populations of both innate and adaptive immune cells, as well as to changes in intestinal permeability.[81] Faecal metabolomic and whole-genome metagenomic studies have revealed significant changes in host gut microbial metabolites and overall bacterial metabolic capacity over the course of GI helminth infections.[82-85] However, knowledge of the exact contribution of gut bacterial metabolism to the regulation of host–parasite relationships and the outcomes of helminth infection is still in its infancy. Hence, a better understanding of the set of bacterial metabolites

involved in the progression of helminth diseases, as well as of the molecular and immune mechanisms underpinning such interactions, is necessary in order for this knowledge to be translated into practical applications.

4 | CURRENT AND FUTURE OPPORTUNITIES FOR THE USE OF BACTERIA-DERIVED PRODUCTS FOR MANAGEMENT AND CONTROL OF HELMINTH INFECTIONS

Investigations of the mechanisms through which probiotic and gut bacteria interact with mammalian cells and regulate host physiology have led to the discovery of several microbial cell structures and metabolites with key roles in host health.[86] Several of these molecules have already been tested for therapeutic applications in GI conditions, with some successes[87–89]; data on the therapeutic utility of others are still preliminary.[90] In the following section, we discuss current perspectives on the application of specific bacterial products to the management and/or control of GI helminth infection and disease.

4.1 | Bioactive bacterial metabolites

The beneficial effects that selected groups of bacteria exert on host health are mediated, at least partially, by molecules derived from their metabolism (e.g., anti-inflammatory SCFAs and lactic acid[32]). Whilst these and other gut microbial metabolites regulate a number of host physiological processes and biochemical functions, rather than disease-specific pathways, they are attracting growing therapeutic interest, for example, in chronic inflammatory GI conditions.[91] For instance, enemas containing sodium butyrate (i.e., the sodium salt of butyric acid, an SCFA with known anti-inflammatory functions) have been tested in both experimental and small-scale clinical studies aimed at treating several GI diseases, including inflammatory disorders and infections by gut pathogens.[87-89] As for the latter, intercaecal infusion of a combination of SCFAs (acetate, propionate, butyrate and valerate) and lactic acid to pigs experimentally infected with the 'nodule worm' *O. dentatum*, resulted in markedly reduced faecal egg counts and worm burdens, compared to untreated controls.[30] The aim of the latter study was not to assess the therapeutic efficacy of SCFAs and lactic acid for the treatment of helminth infections, but rather to explore the relationship between enhanced intestinal production of these metabolites and previously observed reduced worm burdens in *O. dentatum*-infected pigs fed a diet containing prebiotic inulin.[35] Remarkably, natural (i.e., diet-unrelated) increases in both SCFA-producing bacteria and SCFA concentrations were observed in the gut of mice infected with *H. polygyrus*, and linked to long-term parasite survival.[18] Moreover, oral supplementation of mice with isovaleric acid—whose levels are increased in the small intestine of *H. polygyrus*-infected rodents—resulted in enhanced worm fecundity, although no significant changes in worm longevity were observed.[92] Again, these discrepancies point towards varying responses of helminth infections to SCFA administration and call for further studies on the mechanisms underpinning these interactions before translational research programmes can be considered.

The roles played by other gut bacteria-derived metabolites during GI helminth infections, such as amino acids and their derivatives,[91] are as yet poorly understood, and no data are currently available that support their use for the amelioration of helminth diseases.

4.2 | Postbiotics

Aside from bacterial bioactive metabolites, preparations of whole inactivated microorganisms or microbial cell components with beneficial properties to host health, that is, postbiotics, are increasingly being investigated in both the pharmaceutical and food industries.[93] Since postbiotics do not contain live microorganisms, their therapeutic effects do not rely on the ability of ingested bacteria to colonize the host gut, grow in sufficient amounts, and perform specific biological functions. Moreover, postbiotic cocktails can be accurately defined and quantified, and are usually more stable than probiotics when stored.[93,94] The latter attribute is of particular interest for applications of bacterial-based therapeutics to the management, treatment and/or control of human helminthiases in endemic areas, where cold storage facilities are often limited.

Recent studies have demonstrated the therapeutic potential of inactivated asporogenous *B. thuringiensis* producing nematocidal Cry5B against several GI worms.[95–97] Oral administration of Cry5B as cytosolic crystals in inactivated *B. thuringiensis* has shown potent anthelmintic activity against several GI nematodes, including *H. contortus* (in sheep[95]), *A. suum* and *Parascaris* spp. (in pigs and foals, respectively[96]) and the human hookworms *Ancylostoma ceylanicum* and *N. americanus* (in rodent models of infection[97]). Moreover, Cry5B delivery through inactivated rather than live bacteria overcomes environmental concerns linked to the potential spread of transformed *B. thuringiensis* in soil, which may subsequently lead to the selection of Cry5B-resistant worm strains through continued exposure of free-living developmental stages to these bacteria.[96]

Whilst available postbiotics mainly include inactivated probiotic bacteria and bacterial lysates,[93] current trends in beneficial microbe research point towards bacterial extracellular vesicles (BEVs) as a promising source of novel postbiotic formulations.[98] BEVs are membrane-derived nanoparticles, secreted by Gram-negative and Gram-positive bacteria, that constitute an integral component of an evolutionarily conserved mechanism for intercellular communication both in prokaryotes and eukaryotes.[99] Indeed, the secretion of extracellular vesicles (EVs) by bacterial cells and their role(s) in bacteria–bacteria interactions (i.e., quorum sensing, biofilm formation and material exchange) has been well documented for over 40 years (reviewed in Kim et al.[100]). EVs from pathogenic bacteria may contribute to the immunopathology of infection.[101] Moreover, recent studies have shown that EVs from gut-resident bacteria can interact directly with host cells (e.g., via cell surface receptors, or once internalized

through different pathways) and modulate gut immunity, as well as the integrity of the intestinal epithelial barrier (reviewed by Díaz-Garrido et al.[98]). Gut-stemmed BEVs can also translocate through the intestinal epithelium and reach distal organs via the bloodstream.[98]

Although many technical difficulties and challenges are yet to be fully overcome (e.g., optimization and standardization of bacterial culture conditions and EV purification methods) bacterial vesicles from gut-associated and probiotic bacteria are increasingly attracting attention from researchers and industry stakeholders due to their potential use in medical and/or pharmaceutical applications (i.e., as postbiotics). In particular, several studies have focused on the immunomodulatory properties of these BEVs and their ability to ameliorate inflammatory conditions, such as inflammatory bowel disease[102] and food allergy[103] in mice. Additionally, bacterial vesicles can mediate immune-unrelated health-promoting effects.[104-106] For instance, EVs from *Lacticaseibacillus casei* BL23 mimicked the effects of whole bacteria on gut motility,[104] and vesicles secreted by *Akkermansia muciniphila* enhanced intestinal barrier integrity and improved glucose tolerance in a mouse model of diabetes.[105]

The applicability of BEV-based postbiotics against helminth infections has yet to be investigated; however, both their health-promoting and immunomodulatory effects make these bacterial nanoparticles worth pursuing. In this regard, BEVs from *Lactobacillus sakei* increase the production of IgA in Peyer's patches, thus enhancing mucosal immune responses; for this reason, these vesicles have been proposed as potential adjuvants against intestinal infections.[107] Similarly, BEVs exert specific effects on several cell types, including mast cells, dendritic cells and T cells[102,103,108] that could, potentially, improve host responses against helminths. Furthermore, given the ability of gut-microbiota-derived EVs to interact with mammalian (i.e., host) cells, it is tempting to speculate that these vesicles might also be internalized and thus directly interact with other eukaryotes, such as helminths.

5 | CONCLUDING REMARKS

The emergence of anthelmintic resistance, along with the current lack of highly efficient vaccines to prevent helminth infections of humans and animals, is hindering our ability to efficiently and effectively control these diseases. Amid these challenges, microbiota-targeting therapies, along with other bacteria-based interventions (e.g., bacterial vaccines and administration of bioactive bacterial products) have emerged as promising tools that might lead to improved treatment and vaccine outcomes. However, in order to fully explore the applicability of these interventions to 'real-world scenarios', a number of obstacles must be overcome. These include (i) the highly variable efficacy of current microbiota-manipulation strategies, (ii) the extensive biological diversity across host-helminth systems, and (iii) our yet limited understanding of host–(parasite-)microbiota interactions at the molecular level. Advancing our knowledge of the mechanisms underpinning the interactions between helminths, their mammalian hosts and the host gut microbiota will pave the way to new opportunities for the use of selected bacteria and/or bacterial and dietary products in the global fight against parasitic worms. Further development of synthetic biology and optimization of currently available molecular tools to carry out targeted, stable and safe modifications of gut microbiota composition and/or function will also be pivotal. The integration of knowledge acquired in these two areas of research will likely enable to fully exploit the potential of microbiome-based interventions, and their translation into novel and reliable practises for the management and control of helminth diseases of humans and livestock.

AUTHOR CONTRIBUTIONS

Alba Cortés conceived and designed the article. James Rooney, Cinzia Cantacessi, Javier Sotillo and Alba Cortés drafted the manuscript, and Cinzia Cantacessi and Alba Cortés critically reviewed the text. All authors read and approved the final manuscript before submission.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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