Use of Prebiotics and Probiotics for the Control of Cryptosporidiosis

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Abstract

Cryptosporidiosis is an important zoonotic disease which causes significant losses on both humans and animal sides. The economic impact of this disease is also devastating and control of this fatal disease is very difficult as there are no vaccines available for the prevention and only few therapeutic measures are done against this disease. Probiotics and prebiotics are largely used for the purpose of treatment and prevention of several microbial agents including parasitic infections. The objective of this chapter is to explore the use of probiotics and prebiotics against cryptosporidium as there are several types of probiotics used against *Cryptosporidium*. The mechanism of actions through which probiotics act against parasites and provide significant beneficial effects to the host. There is no significant work done on the use of prebiotics for the treatment and control of cryptosporidium. The one health approach for the control of cryptosporidium is also considered a primary way to control the zoonotic impact of this infection.

Keywords: Cryptosporidiosis, Control, Prebiotics, Probiotics, Animals, and humans.

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Introduction

Cryptosporidiosis is known as a fatal diarrheal illness in both humans and animals all around the world. Children and individuals with compromised immune systems are at higher risk of getting this disease (Figure 1). Cryptosporidiosis was first considered as a dangerous disease for human health in the 1980s after the epidemic of AIDs (Wang et al., 2018). The global prevalence of cryptosporidiosis was 10.9% in the individuals with combined infection of HIV as estimated from 2007 to 2017 (Mekonnen et al., 2016). An epidemiological study conducted on a large scale in sub-Saharan Africa and Southeast Asia including 22500 children found that the major reason for severe diarrhea in children with significant risk of death is cryptosporidium (Kotloff et al., 2013). As a foodborne pathogen, *Cryptosporidium* is also known for causing almost 8 million cases of food borne infections yearly (Koutsoumanis et al., 2018; Ryan et al., 2018). As a gastrointestinal pathogen, the burden of this disease in different studies mainly focuses on acute infections, calculated that 4.2 million disability adjusted life years are lost in children under five years of age with growth faltering and cognitive defects (Khalil et al., 2018). The disease impact studies in developed countries revealed that this disease causes acute illness with persistent abdominal pain, arthralgia, fatigue, irritable bowel syndrome (Insulander et al., 2013; Stiff et al., 2017) and also associated with human colon cancer as shown in a recent study (Osman et al., 2017). In animals, *Cryptosporidium* is the main cause of diarrheal illnesses in neonatal calves and other animals. In an economical way, this disease affects cattle industry as it causes production losses due to the death of young calves, cost of diagnostic methods, treatment and supportive therapies and also the cost of feed and husbandry so that the animal achieves market weight (Olson et al., 2004). The study of cattle infected with *Cryptosporidium*, as observed from birth to 210 days, revealed a relationship between infection and less weight gain and lower production rate (da Silva Abreu et al., 2019). In Australia, it was reported that the acute infection of *Cryptosporidium* causes production impacts on growth and carcass weight in lambs on sheep farms (Jacobson et al., 2016). As a waterborne illness, the outbreaks of *Cryptosporidium* due to contaminated water supplies also causes severe health impacts as well as economic losses. It is reported that the outbreak of waterborne *Cryptosporidium* causes illness in 403000 people and causes a significant loss of USD 96.2 million in Wisconsin and also affects 45% of the population of 60000 residents of Sweden (Corso et al., 2003; Ridderstedt et al., 2018). Detection of oocysts of cryptosporidium in public water supplies ultimately resulted in condemnation of supplies and reported in Ireland, an outbreak costing EUR 19 million (Chyzheuskaya et al., 2017).

Probiotics

According to the World Health Organization (WHO), probiotics are defined as "live organisms which provide health benefits to the host when administered in adequate amounts" (Hill et al., 204). Probiotics work to modulate the immune response of the host and provide health benefits during the attack of pathogens (Wu et al., 2019). Coordinating with the epithelial cells in the gastrointestinal tract, such as

Payer's patches, host immune cells, and M cells, led to the enhancement of the number of cells which produce IgM, IgA, and secretory IgA (Szajewska et al., 2001). Probiotics also have an influence on dendritic cells, which help in the differentiation of the T helper cells (T regulatory lymphocytes) including Th1 and Th2 resulting in the modulation of production of cytokines such as TNF-α IFN-γ and IL-10, IL-12. They also help to balance between immoderate and required defense mechanisms (Resta-Lenert & Barrett, 2003; Kaji et al., 2018; Mandal et al., 2024). Probiotics (live bacterial cell supplements) have been studied to evaluate their effects on parasitic infections (Table 1) (Travers et al., 2011). For the treatment of acute diarrheal infections, probiotics were used and gave successful outcomes and in several animal models, probiotics also show significant effects against cryptosporidiosis (Pickerd & Tuthill, 2004). In another study, probiotics used in experimentally infected mice with *Cryptosporidium*, the duration and number of oocysts decreases (Alak et al., 1997) and it also decreases the viability of the oocysts in in vitro examination (Foster et al., 2003; Guitard et al., 2006). The probiotic mixture containing *Lactobacillus casei*, there was no significant activity against *Cryptosporidium* in experimental conditions, in addition to that the oocysts clearance was more rapid in mice treated with probiotics as compared to the control group. The lactic acid bacteria are seen to hinder the process of encystment of the parasite as *Cryptosporidium* oocysts require an alkaline medium for this process which results in decreased viability of the oocysts (Smith et al., 2005; Del Coco et al., 2016). Probiotics also have beneficial impacts on mucosal and systemic immunity, both innate and acquired immunity. It is thought that the host microbiome protects against the colonization of *Cryptosporidium spp.* (Negatu et al., 2020). In an experiment, the duration and number of *Cryptosporidium parvum* oocysts decreases, shed in the feces of mice, as treated with *Lactobacillus acidophilus* and *Lactobacillus reuteri* (Alak et al., 1999). It has been reported that the use of *L. reuteri* as a probiotic enhances the proliferation of intestinal epithelium, helps in repairing the damaged epithelium, and finally decreases inflammation (Wu et al., 2020). On the human side, the administration of probiotic strain DSM 17938 of *L. reuteri* has demonstrated both safety and acceptability in infants (Hoy-Schulz et al., 2015). The use of *L. acidophilus* LB in experimental mice infected with *C. parvum*, show reduction in the number of oocysts count up to 95.77% (Darwesh & El-Sayed, 2022; Gaber et al., 2022).

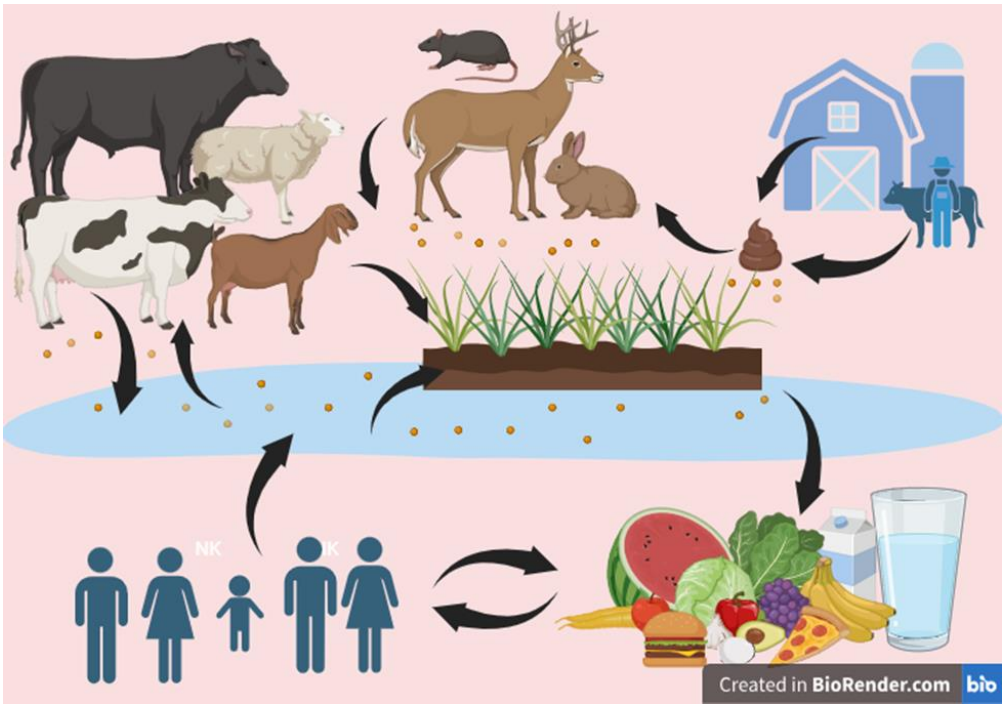

Fig. 1: Transmission of *Cryptosporidium* among humans, animals, and environment.

Table 1: Types of probiotics used against *Cryptosporidium parvum*

Probiotics	Host	References
Bifidobacterium breve ATCC15698	Cell culture	(Deng et al., 2002)
L. reuteri ATCC23272	Cell culture	(Foster et al., 2003)
Limosilactobacillus reuteri 4000, 4020	Mouse	(Alak et al., 1997)
L. acidophilus NCFM	Mouse	(Alak et al., 1999)
Brevibacillus brevis, Enterococcus faecium, Pseudomonas alcaligenes	Cell culture	(Foster et al., 2003; Glass et al., 2004)
L. reuteri 4000, 4020	Mouse	(Waters et al., 1999)
i Shirota	Neonatal	(Guitard et al., 2006)
Lacticaseibacillus rhamnosus GG + L. case	Human	(Pickerd & Tuthill, 2004)
Actimel	Calf	(Harp et al., 1996)

Mechanism of Action of Probiotics

There are several mechanics through which probiotics act and provide beneficial effects to the host (Figure 2). Against parasites, probiotics work by increasing the population of beneficial microorganisms, these microorganisms include bifidobacteria and lacto-bascilli as these

microorganisms compete with harmful pathogens in the gastrointestinal tract (Gupta & Garg, 2009). Another mechanism of action of probiotics is the production of several antibacterial agents including bacteriocins, organic acids such as lactic acid, butyric acid, and acetic acid, that have considered possess antiparasitic activities (Cleusix et al., 2008). Probiotics also promote the immunological responses of both innate and adaptive responses of the host (Konstantinov et al., 2008). There is limited research data available on the action of probiotics against parasitic infections. The data available is mostly on model animals such as mice or susceptible animals.

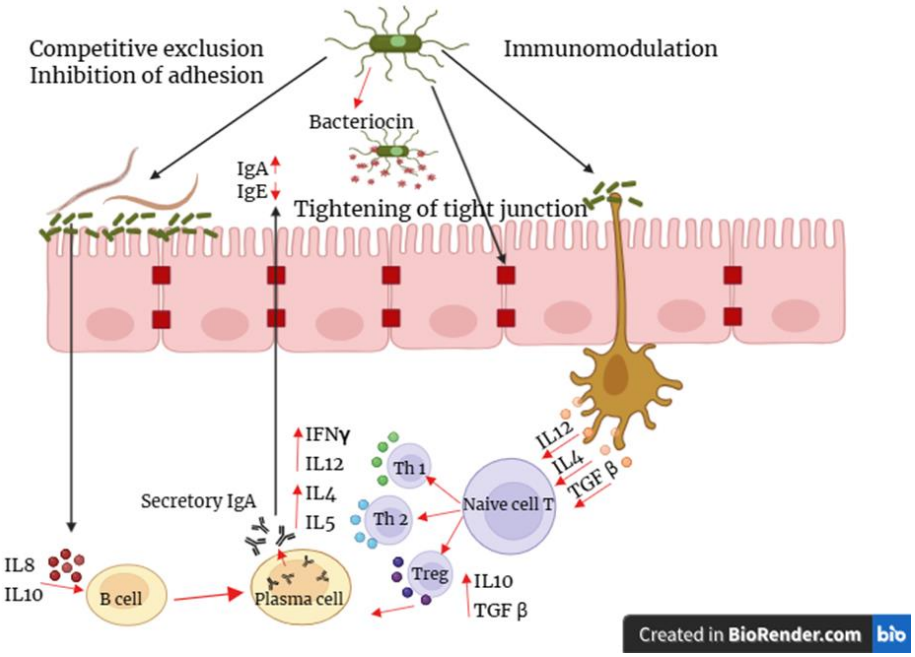

Fig. 2: Mechanism of action of probiotics. Four major actions include competition for nutrition and adhesion with pathogens, secretion of bacteriocin (antimicrobial substances), tightening the cell junctions to provide stronger barrier, and modulation of immune responses.

Prebiotics

The concept of prebiotics was first introduced by Glenn Gibson and Marcel Roberfroid in 1995 (Gibson & Roberfroid,1995). Prebiotics are defined as non-digestible food ingredients which provide beneficial effects to the host particularly by stimulating the activity or growth of a specific bacteria in the colon and which ultimately improve the host health (Davani-Davari et al., 2019; Gibson et al., 2010). For almost 15 years, prebiotics were defined according to this definition. Only few compounds of carbohydrates are classified as prebiotics according to this definition, for instance short and long chain β-fructans (FOS and inulin), lactulose, and GOS (Galacto-oligosaccharides). Prebiotics were redefined as "selective fermented ingredients that provide beneficial outcomes to the host while changing the composition or activity of intestinal microbiota" in the 6th meeting of international scientific association of probiotics and prebiotics (ISAPP) in 2008 (Foster et al., 2019). Prebiotics have been used in history for their several beneficial functions such as immune modulation, enhancing the bioavailability of minerals, inhibition of the infections of gastrointestinal tract, regulation of metabolic diseases, and modifications of inflammatory conditions. Prebiotics affect the microbial activity on the luminal and mucosal surfaces and enhance the positive interactions of host and microbe (Roberfroid et al., 2010). All the prebiotics are fiber but it is important to note that not all the fibers are prebiotics. It is important that prebiotics provide benefits to the health of animals. They are important equally for both the health of animals and humans (Gibson et al., 2017). It has been seen that mice inoculated with insulin, have high numbers of gut microbiota such as *Actinobacteria* and *Akkermansia muciniphila*, also higher concentration of short chain fatty acids, indicating beneficial impacts of prebiotics. Serological testing revealed that the use of insulin against parasitic infection of *Trichinella muris* resulted in the significant reduction of the type-2 immune response, which indicates that instead of increasing the immune response, prebiotics inhibited the immunological response against the infection. In another study, mice infected with *Trichinella spiralis*, when given β-glucans show significant improvement as β-glucans enhance the proliferation of *Akkermansia muciniphila*, ultimately initiating the TLR2-dependent immune response which increases the explosion of worms (Jin et al., 2022). It has been reported that the use of prebiotic insulin in malnourished mice show significant results against the infection of *Giardia* such as it decreases the severity of parasitic infection, enhances body mass and increases the number of lactobacilli in the feces. Additionally, the comparison of mice fed with prebiotics and the starved mice infected with *Giardia*, administration of prebiotics significantly increased the antibody production against *Giardia* such as IgA and IgG, and production of cytokines for instance IL-6 and IL-10. The level of nitric oxide was also enhanced and this study was the only effort to the prebiotics effect on immunological function and morphology of the gut (Shukla et al., 2016). There is a need for further research to find out the significant impacts of prebiotics against different parasitic infections including cryptosporidiosis.

One Health Approach for Prevention of Cryptosporidiosis

The One Health approach to solve the issue of zoonotic diseases and improvement of health is a strategy which is used globally at the interface of human-animal-environment. One Health approach demands collaboration between different health sectors including veterinarians, health physicians, and public health operators to control the infection by focusing on betterment of the educational system, knowledge and thinking status, rules and legislation, and administrative structures (Fawzy & Helmy, 2019). This approach has been previously used for the

prevention and control of cryptosporidiosis and several other zoonotic diseases (Feng et al., 2018; Fawzy & Helmy, 2019; Helmy et al., 2020; Innes et al., 2020) which demands a close one health interaction among professionals working in different health related fields such as physicians, veterinarians, diagnosticians, epidemiologists, public health experts, ecologists, economists, social scientists, governments, decision-makers, and pharmaceutical industries. The one health strategy used for the control of cryptosporidiosis in humans, animals, and environmental bodies by understanding the pathogenesis of the parasite, its life cycle, sources of transmission, highly susceptible risk group in population, diagnostic methods, treatment and vaccination regimen. The main strategy of control should focus on increasing the awareness and knowledge about cryptosporidiosis and its route of transmission, break the transmission cycle, epidemiological approaches to identify risk factors, establishment of surveillance program, treatment options to control outbreaks, and training of the medical personnel regarding diagnosis of the parasite (Kay et al., 2012; Sparks et al., 2015; Chalmers et al., 2018).

Conclusion

Despite the fact that *Cryptosporidium* was discovered almost a century ago, the control of this parasite is still difficult. The research for the innovative treatment therapies against cryptosporidiosis has been slow on both sides, animals and humans. It is thought that the lack of therapeutic measures against this illness is attributed to the limited knowledge about the cellular and molecular interactions between host and parasite in the gut mucosa during the early stages of infection. Probiotics and prebiotics are used against several parasitic infections but there is a need for in-depth research to explore the pathogenesis of the parasite and role of probiotics and prebiotics in the control of cryptosporidiosis. Most of the research has been done on mice so there is an urgent need for a more relevant host for further investigations. It is also important to identify the factors such as resistance and recovery from infection which will help to develop more effective control and prevention of the important disease.

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