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Review Article

The Role of *Lactobacillus* Probiotics in Dysentery

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Abstract

Dysentery is a gastrointestinal infection characterized by mucus and blood with stool usually caused by bacteria and parasites from contaminated food and water with faeces. The disease is widely recorded in developing countries, especially with poor health and hygiene conditions. Shigellosis and amoebiasis are two major types of dysentery that cause upsetting gastrointestinal microbial flora essential for proper digestions. Diarrhoea, pain, fever, and feeling of incomplete defecation are common symptoms of dysentery. Probiotics, especially *Lactobacillus spp.* are currently used in diarrhoea and indigestions to improve digestive health, grow immunity, and general well-being. The actual mechanism of action of *Lactobacillus spp.* is still not precise in the literature. In this review, we summarise the findings of recent studies based on the roles of *Lactobacillus spp.* in the management of pathogens of bacillary and amoebic dysentery in clinical, preclinical, and *in vitro* studies.

Keywords: *Diarrhoea; Dysentery; Probiotics; Lactobacillus; Shigellosis; Amoebiasis*

Introduction

Dysentery is an infection caused mainly by bacteria or amoeba in the gastrointestinal tract, usually characterised by symptoms of bloody diarrhoea, mucus with stool, feeling of incomplete defecation, pain, or fever [1,2]. It is classified mainly as bacillary or amoebic dysentery depending on the causative microorganisms [1].

Shigellosis or bacillary diarrhoea is caused by *Shigella* (family: Enterobacteriaceae). *Shigella dysenteriae* and *S. flexneri* incite severe infections to lead to epidemic bacillary diarrhoea or dysentery in developing countries and causes over a million deaths every year [3, 4]. Briefly, the bacteria enter into the gut lumen via microfold cells [5]. *Shigella* triggers apoptosis of macrophages and defends it against submucosal macrophages [5, 6] (Figure 1A). The bacteria also induce mitochondrial damage and apoptosis of non-myeloid epithelial cells [7]. The death of macrophages and epithelial cells causes the release of cytokines and induces mucosal inflammatory responses or shigellosis [7, 8] (Figure 1A). Shigellosis treatment is often unsuccessful, as *Shigella* becomes resistant to several antibiotics like ampicillin, co-trimoxazole, tetracyclines, and nalidixic acid. World Health Organization (WHO) recommends oral ciprofloxacin as the first-line treatment and azithromycin, ceftriaxone, or pivmecillinam as a secondary drug choice for antibiotic-resistant *Shigella* species [9]. Antibiotic

treatment in the clinic potentially induces gut dysbiosis or changes in the gut microbial flora that favours the harmful bacteria that cause inflammatory diarrohea and dysentery [10-14].

Amoebiasis or amoebic dysentery is mainly caused by *Entamoeba histolytica* (Figure 1B), which is more prevalent in developing countries [15, 16]. Food or water contaminated with faeces containing *E. histolytica* cysts mainly spread the disease, as some of these countries have poor management of sanitation systems, a large population, and tropical climatic conditions [15, 17]. People infected with *E. histolytica* are mostly asymptomatic (80 - 90%) [15], and consequently, treatment starts at a later stage with severe conditions. *Entamoeba histolytica* causes degradation of the mucosal layer (by releasing different enzymes), adheres to the intestinal epithelium, and invades into various tissues (e.g. blood, liver, lungs, brain) by suppressing the host's immune system [18] (Figure 1B). Metronidazole, secnidazole, tinidazole, ornidazole, and nitazoxanide are commonly used drugs to treat amoebiasis. Unfortunately, most of these drugs display side-effects, like nausea and vomiting [15].

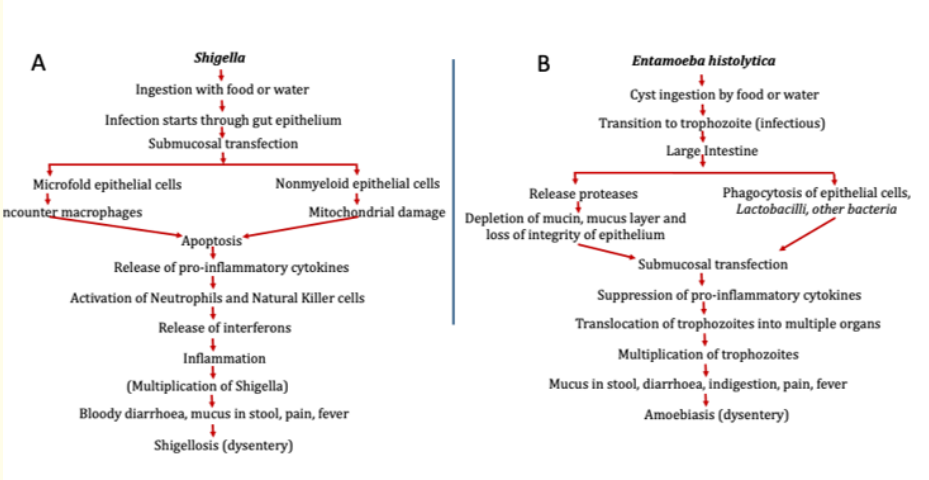

Figure 1: *Mechanisms of shigellosis (A) and amoebiasis (B).*

Treatment of dysentery

Repeated treatment of antibiotics causes changes in gut microbiota, as antibiotics can kill both pathogenic and non-pathogenic bacteria. The treatment with antibiotics also favors a suitable environment for the growth of antibiotic-resistant bacteria. *Shigella* spp. and *Entamoeba* are getting resistant to various antibiotics or antiprotozoal drugs [14, 19, 20]. This magnitude of resistance also varies from individual to individual. An alternative treatment strategy is required urgently [14]. Non-therapeutic management like hand-hygiene, proper disposal of faecal waste, sewerage water management, ensuring the supply of clean drinking water, and a healthy diet can potentially prevent the magnitude of epidemic situations of amoebiasis in the developing countries [15]. Preventing contamination from faecal to oral transmission, covering food from flies, proper hand-hygiene may reduce the spread of *Shigella* infections, although the whole mechanism of these diseases is still not clearly understood [9]. The actual prevention of dysentery is a difficult task, and therefore different management strategies are adopted to reduce this disease. One of the commonly used preventative measures is taking probiotic supplements as in pharmaceutical formulations, healthy food digested by non-pathogenic bacteria, probiotic drink, and dairy products, synbiotics (probiotics and supporting non-probiotics to promote the activity of probiotics) with conventional antibiotic treatment [21-23].

Role of *Lactobacilli* on dysentery

Probiotics are live microorganisms (bacteria and fungi) consumed for the improvement of digestions by the restoration of gut flora and general well-being [24,25]. Probiotics may contain bacteria such as *Lactobacillus* and *Bifidobacterium* or yeasts like *Saccharomyces boulardii* [25]. *Lactobacillus* is one of the widely used microorganisms as a probiotic, and the co-treatment of antibiotic formulation showed the desired improvement of health outcomes in clinical studies [23, 26]. A previous study identified 16 species of *Lactobacillus* by 16S rRNA gene sequencing [27]. *Lactobacillus rhamnosus, L. casei, L. acidophilus and Lactobacillus plantarum* are commonly used in probiotic formulations. They showed many beneficial effects against dysentery or bloody diarrhoea *in vitro*, preclinical and clinical studies, and the information is summarised in table 1.

Key Findings:	Ref:
Fermented milk with *Lactobacillus casei* and *L. acidophilus* prevented *Shigella sonnei* induced gastrointestinal infection in mice (preclinical study).	[44]
Two weeks treatment of *Lactobacilli* in weanling pigs improves food intake and reduce *E. coli* numbers from GI tract (preclinical study).	[45]
Lactobacillus rhamnosus release acetic, polyglutamic, formic and lactic acids. *L. rhamnosus* possesses antimicrobial properties against *Salmonella* (*in vitro* study).	[36]
Lactobacillus casei reduced transcriptions of cytokines and chemokines produced by *Shigella flexneri*. It also prevented the release of *Shigella flexneri* secreted adherence molecules for infection (*in vitro* study).	[46]
Co-treatment of *Lactobacillus rhamnosus* and Lactobacillus acidophilus provided protection against Shigella dysenteriae in rat (preclinical study).	[47]
Lactobacillus spp reduced aggregation of *Brachyspira hyodysenteriae* and *Brachyspira pilosicoli in vitro*.	[48]
Lactobacillus plantarum lipoteichoic acid reduced production of Shigella flexneri peptidoglycans (an inflammatory agent).	[49]
Frequent episodes of *Entamoeba histolytica* induced dysentery causes depletion of essential gut bacteria that leads to poor digestions and absorption of food from intestine. *Entamoeba histolytica decreases Lactobacillus spp.* and leads to a dysbiosis stage.	[50]
Lactobacillus casei inhibited growth of *Shigella sonnei* and *Shigella flexneri* (in vitro study).	[51]
Reduced faecal *Lactobacillus spp* was observed in asymptomatic dysentery patients.	[52, 53]
Lactobacillus rhamnosus GG and fructo-oligosaccharides once daily for 3 days (plus oral ciprofloxacin 15 mg/kg twice daily for 3 days) with children experiencing bacillary dysentery. Probiotic treatment reduced the duration of dysentery and fever. It did not reduce the duration of hospital stay.	[23]
Clinical trials for 5 days treatment with a probiotic cocktail (contained *Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium infantis, Bifidobacterium breve,* and *Streptococcus thermophiles*) reduced dysentery and duration of hospitalisation in patients against placebo control.	[26]
Lactobacillus pentosus, L. paraplantarum and *L. rhamnosus* showed effectiveness to prevent *Shigella dysenteriae* in rat macrophage *(ex vivo).*	[54]
Lactobacillus casei and *Entercoccus faecium* reduced the survival of *Entamoeba histolytica in vitro*.	[55]
Patients with GI disorders have dysentery and gut dysbiosis. Probiotics and Fecal Microbial Transplants were shown to be beneficial against conventional antibiotic therapy.	[56]
Lactobacillus spp excrete reduced the size and morphometric alterations of cell membrane of trophozoites of *Entamoeba histolytica in vitro.*	[57]
Entamoeba histolytica caused phagocytosis of gut *Lactobacillus spp*.	[58]
Lactobacillus acidophilus attenuated Shigella dysenteriae toxins (*in vitro*).	[59]
Exopolysaccharides produced by *Lactobacillus plantarum* prevented biofilm formation of *Shigella flexneri* by decreasing the polysaccharide production of its extracellular polymeric matrix.	[60]
Shigella infection decreased the content of *Lactobacillus* but increased abundance of *Shigella* or *Escherichia* in the gut. Parenteral infection of *Shigella* caused serious consequence than oral infection in mice, as gut microbiota prevented *Shigella* translocation (preclinical study).	[61]
Lactobacillus curvatus released 34 organic acids and it produced 248.4 mmol/L lactic acid after 48 h of fermentative growth and it showed antibacterial activity (*in vitro* study).	[35]

Table 1: *Recent updates on the roles of Lactobacilli on dysentery.*

In brief, *Lactobacilli* works against dysentery in several ways (Figure 2). Firstly, they work for their colonisation over the gastrointestinal lumen over the non-myeloid epithelial cells and compete for their nutrients with dysenteric bacteria like *Shigella, Salmonella* and *Escherichia coli* [28]. The colonisation of *Lactobacilli* increases the integrity of the epithelial cell layer. Thus, epithelium becomes less susceptible to *Shigella, E. coli,* or *Entamoeba* infection and their penetration into the intestinal lumen [29-34]. Once the gut flora of *Lactobacilli* is well established, the bacteria release multiple short-chain fatty acids like lactic, acetic, polyglutamic, and formic acid that supply nutrients to the host as well as lowers the pH of the intestinal lumen [35-37]. As a result, it creates an unfavourable environment for *Shigella* or *Entamoeba* for their growth and multiplications. *Lactobacilli* also prevent the phagocytosis process of macrophages in the gastrointestinal lumen caused by *Shigella* and thereby prevents the excess release of cytokines and chemokines, which causes gastrointestinal inflammation. Thus, *Lactobacillus* also acts as anti-inflammatory agents in the gut. The bacteria also act as an antimicrobial agent against different microorganisms [35, 38, 39]. *Lactobacilli* also synthesizes many short-chain fatty acids and vitamins that help a healthy gut environment and meet people's dietary needs. Different byproducts of *Lactobacilli* also prevent the generation of essential cellular parts of *Shigella,* such as polysaccharides produced by *Lactobacillus plantarum* prevents the synthesis of the extracellular matrix of *Shigella*.

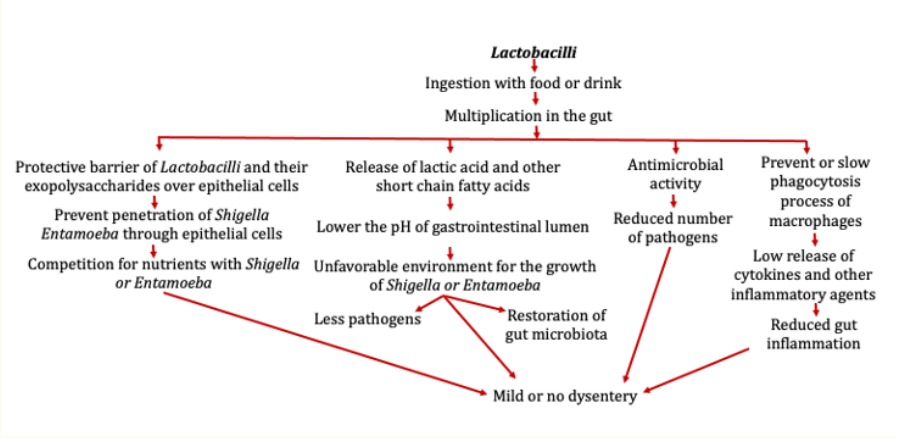

Figure 2: *Overall roles of Lactobacilli in the management of dysentery.*

Conclusion

The use of probiotics is beneficial for the management of dysentery or bloody diarrhoea, but reports related to the adverse effects are warranted. *Lactobacillus* bacteremia (bacteria in the bloodstream) and liver abscess are rare but reported in the clinic [40-42]. A high dose of *Lactobacillus rhamnosus* caused diarrhoea and reduced the count of colonic *Lactobacillus* and *Bifidobacterium* in piglet [43]. Long-term treatment of probiotics with a high dose of some *Lactobacillus spp.* may cause harm in some individuals and animals. Regular health checks and proper diagnosis can prevent the situations like bacteremia, organ failure or massive changes in gastrointestinal flora. Overall, *Lactobacilli* should be considered a useful food supplement with the minimum effective dose to prevent dysentery, support a healthy gut microbiota, and maintain general human well-being.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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