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The Potential of *Leuconostoc mesenteroides* Strain LK-151 to Inhibit *in vivo Salmonella* Infection

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Abstract

The purpose of the study was to evaluate the efficacy of the probiotic *Leuconostoc mesenteroides* strain LK-151 isolated from fermented camel milk against *Salmonella* infection in BALB/c mice. A total of 50 mice were divided into five groups of n = 10 per group and subjected to different treatments. Infecting mice with *Salmonella* led to a significant decrease in feed intake and body weight. This occurred simultaneously with the appearance of symptoms on day 3 of the infection with the recording of one death after 6 days. The pathogenic cells were detected at a high rate in the feces, which reached 7.045 Log_{10} CFU/g on day 7 post-infection. Histological studies revealed significant damage to the ileum and the liver. Whereas, administering mice with the probiotic strain for one week before being infected with *S.* Typhimurium avoided body weight loss, and feed intake was not affected. The probiotic was able to suppress the growth of the pathogen and offer protection to the ileum. However, localized congestion was noted in the liver of some mice. It was also found that giving the probiotic to the mice during the infection did not improve the tested parameters. It can be concluded that the strain under study has probiotic potential and can protect against *Salmonella* infection.

Keywords: BALB/c mice; camel milk; *Leuconostoc mesenteroides* LK-151; preventive effect; probiotic; *Salmonella* Typhimurium

Резюме

Целта на проучването е да се оцени ефикасността на пробиотичния щам *Leuconostoc mesenteroides* LK-151, изолиран от ферментирало камилско мляко, срещу инфекция със *Salmonella* при BALB/c мишки. Общо 50 мишки са разделени на пет групи от n=10 в група и са подложени на различни третирания. Заразяването на мишките със *Salmonella* доведе до значително намаляване на приема на храна и телесно тегло. Това се случи едновременно с появата на симптоми на третия ден от инфекцията, като след 6 дни е регистриран един смъртен случай. Патогенни клетки са открити в изпражненията във висока степен - до 7.045 Log_{10} CFU/g на 7-ия ден след заразяването. Хистологичните изследвания показват значително увреждане на илеума и черния дроб. При третирането, обаче на мишките с пробиотичния щам в продължение на една седмица преди да бъдат заразени със *S. typhimurium*, се избягва загубата на телесно тегло, а приемът на храна не се повлиява. Пробиотикът е в състояние да потисне растежа на патогена и да осигури защита на илеума. Въпреки това, в черния дроб на някои мишки е отбелязано локално претоварване. Установено е също така, че приемането на пробиотика от мишките по време на инфекцията не води до подобряване на изследваните параметри. Може да се заключи, че изследваният щам притежава пробиотичен потенциал и може да предпазва от инфекция със *Salmonella.*

Introduction

Salmonella is one of the most common causes of human foodborne illness. There are two types of *Salmonella* infection; non-typhoid and typhoid fever (Setyawardani *et al*., 2017; Gut et *al*., 2018). Non-typhoidal *Salmonella* (NTS) infections are of global concern, causing symptoms ranging from limited gastroenteritis to life-threatening bacteremia (Kubicek-Sutherland *et al*., 2021). NTS in-

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fections are responsible for 90 million cases and 155,000 deaths worldwide annually (Bula-Rudas *et al*., 2015). It usually occurs as a result of improperly handled food that has been contaminated with human or animal feces (Harish and Menezes, 2015).

The overuse of antibiotics has led to their becoming less effective against several pathogenic strains, including *Salmonella* species. The emergence of antibiotic-resistant bacteria thus requires the development of new antibacterial substances to prevent and treat infections caused by enteric pathogenic bacteria (Nami *et al*., 2015; Gut *et al*., 2018; Sikarchi and Fozouni, 2018). Among these compounds, probiotics have been identified as a promising solution in both the preventive and therapeutic treatment of *Salmonella enterica* serovar Typhimurium (Shi *et al*., 2020). According to the Food and Agricultural Organization/World Health Organization (FAO/WHO), probiotics were defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host" (Brown and Valiere, 2004). Most of the probiotic strains belong to the *Lactobacillus* and *Bifidobacterium* genera (Grimoud *et al*., 2010). A number of other LAB genera were employed, such as *Enterococcus*, *Streptococcus*, and *Leuconostoc* (Abdollahi *et al*., 2016).

Numerous health benefits have been attributed to probiotic bacteria, including prevention and treatment of diarrheal diseases (including acute infantile diarrhoea, antibiotic-associated diarrhoea, and nosocomial infections), reduction of serum cholesterol, prevention of systemic infections, enhancement of the immune response, prevention and treatment of allergies, anticancer effects, and alleviation of lactose intolerance (Kechagia *et al*., 2013; Bajaj *et al*., 2015).

To select a microorganism as a probiotic, there are several important criteria, including viability and survival during intestinal passage, ability to adhere to the gastrointestinal mucosa, unable to transfer genetic resistance elements to the intestinal host, and safety assessment (Bermudez-Brito *et al*., 2012; Muryany *et al*., 2017; de Melo Pereira, 2018). Furthermore, the protective activity of probiotic bacteria against gastrointestinal infections and the related mechanisms have received special attention, as this interaction has been utilized as a criterion for the selection of novel probiotics for human use (Singh *et al*., 2014).

In this regard, *Leuconostoc mesenteroides* strain LK-151, isolated from Algerian fermented camel milk, has been shown to have important probiotic potential *in vitro* in a previous study (Bouguerra *et al*., 2020). In the present work, we aimed to evaluate the effectiveness of the probiotic strain at inhibiting *S. enterica* subsp. *enterica* Serovar Typhimurium Strain ATCC 13311 in BALB/c mice.

Materials and Methods

Breeding

Fifty BalB/c haloxenic male mice, weighing about 18–27 g, from a conventional type of breeding were purchased from the Pasteur Institute-Algiers and handled in accordance with the Canadian Guide for Laboratory Animal Care and Use (Canadian Council on Animal Care, 1993). The pathogen-free animals were housed in a temperature-controlled room at 22°C under a 12 h light/dark cycle and supplied with potable water and commercial animal feed *ad libitum*.

Bacteria and growth conditions

S. enterica subsp. *enterica* Serovar Typhimurium Strain ATCC 13311 was grown in brain-heart infusion broth (BHI) medium at 37°C for 24 h. The bacterial suspension was washed twice in PBS buffer (pH 7.2) and adjusted to 8 Log_{10} CFU/ml (OD: 0.15 at 630 nm), the dose of which is equivalent to LD 50 (Bae *et al*., 2003; Andino *et al*., 2014).

L. mesenteroides strain LK-151 was previously isolated from fermented camel milk and identified by sequence analysis of the amplified 16S rRNA gene product. The strain exhibits beneficial probiotic traits such as adherence properties and acid and bile tolerance. The bacterial strain also demonstrates *in* v*itro* antagonistic activity toward certain pathogenic bacteria, including the tested strain *S. enterica* subsp. *enterica* Serovar Typhimurium strain ATCC 13311 (Bouguerra *et al*., 2020). The frozen culture of the probiotic was reactivated in MRS broth at 30°C for 24 h, washed twice, recovered in PBS buffer (pH 7.2), and adjusted at 9 Log_{10} CFU/ ml (OD: 1.46 at 630 nm) (Andino *et al*., 2014).

Experimental design

Fifty mice were used in this study. After one week of acclimatization, mice were randomly assigned to one of five treatment groups of ten mice each:

(1) Negative control group (NC), in this group, the mice were only given 0.2 ml of sterile phosphate-buffered saline (PBS, pH 7.2).

(2) Infected group (I), in this group, the mice were orally received 0.2 ml of *Salmonella* Ty-

phimurium ATCC 13311 once a day for 3 days.
(3) Feeding group (F), in this group, the mice were given 0.2 ml of the probiotic culture once a day for 7 days.
(4) Pre-infected group (Pr-I), in this group, the mice were administered 0.2 ml of probiotic culture once a day for 7 days and then infected with 0.2 ml of *Salmonella* Typhimurium ATCC 13311 once a day for 3 days.
(5) Post-infected group (Ps-I), in this group, the mice were infected with 0.2ml of *Salmonella* Typhimurium ATCC 13311once a day for 3 days and treated with 0.2ml of the probiotic culture once a day for 7 days.

Feed intake and body weight

Feed intake was measured by subtracting the remaining amount not consumed by the mice from the amount provided to the animals. The body weight of the animals was monitored daily, and the mean was calculated for each group throughout the experiment (Gagnon *et al*., 2006).

Counting S. typhimurium ATCC 13311

At 3 and 7 days after challenge with the pathogenic strain, fecal samples, obtained by manually pressing the lower abdomen of 3 mice from groups (I, Pr-I, and Ps-I), were analyzed individually by suspending 50 mg in 0.5 ml PBS buffer (pH 7.2) to obtain a concentration of 100 mg/ml (Gagnon *et al*., 2006). The suspensions were serially diluted 10-fold up to 10^{-6}, and appropriate dilutions were plated in triplicate on SS agar. The inoculated plates were incubated aerobically for 24 h at 37°C, and only black colonies were counted (Bae *et al*., 2003).

Histological examination

At the end of the experiment, five mice from each group were sacrificed by cervical dislocation. Prior to histological examination, the liver and ileum were removed and fixed in 4% formalin. The different organs were cut into small pieces and then dehydrated in a series of alcohol solutions, placed in xylene, and embedded in paraffin. The paraffin blocks were cut by a microtome (Leica, Germany), and the resulting 5-µm-thick sections are rehydrated and then spread on slides that, after drying for 1 hour at 37°C, are stained with haematoxylin-eosin.

Statistical Analysis

All data were subjected to one-way ANOVA using R version 3.5.1. The mean values of treatment groups were compared using the Tukey test, and differences were considered statistically significant at $P<0.05$.

Results and Discussion

Numerous reports have demonstrated the value of probiotics as dietary supplements for controlling pathogenic infections in humans and animals. In this study, the effect of probiotic bacteria, *L. mesenteroides* strain LK-151 on *Salmonella* infection in mice was assessed by monitoring feed intake, body weight, the number of *Salmonella* Typhimurium ATCC 13311 colonies in their feces, and the histological appearance of the ileum and liver.

Feed intake and body weight

Compared with the negative control group, feeding the probiotic bacteria to mice for one week had no significant effect on feed intake (Fig. 1). As well as for the Pr-I group. Nevertheless, after a challenge with *Salmonella*, the feed intake of mice was significantly affected in both the infected and post-infected groups. These findings are in line with those mentioned by Kim *et al*. (2013).

Daily body weight measurements of mice in all groups were performed, and the results are shown in Fig. 2. When mice were given the probiotic (F group), there was no significant effect on the weight gain compared to the NC group. This result is in accord with that reported by El-Jakee *et al*. (2010). However, Kemgang *et al*. (2016) found that the S1K3 probiotic induced an increase in the weight of the mice with a percentage of 22–25% compared to 15–22% obtained with skimmed milk (the control).

The probiotic provided mice in the Pr-I group a defense against weight loss. On days 4 to 7 post-infection, the mice in the infected (I) group

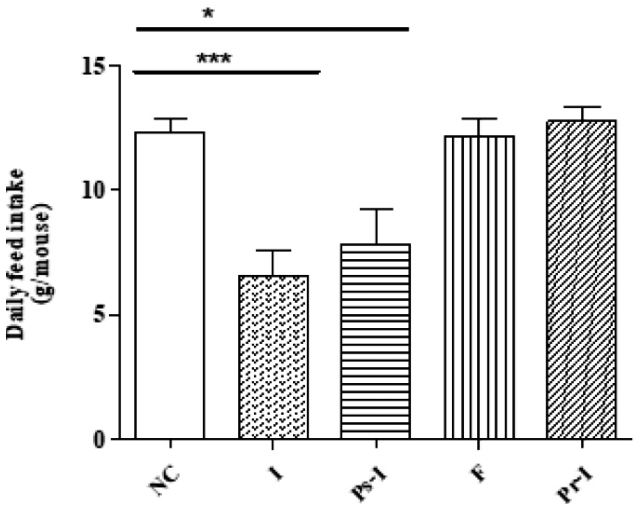

Fig. 1. Total mean feed intake (g/mouse) of mice. Data are means ± SEM, (n=10 mice for each group). *** P<0.001, * P<0.05 (statistical differences within groups). NC: Negative control group, I: Infected group, Ps-I: Post-infected group, F: Feeding group, Pr-I: Pre-infected group.

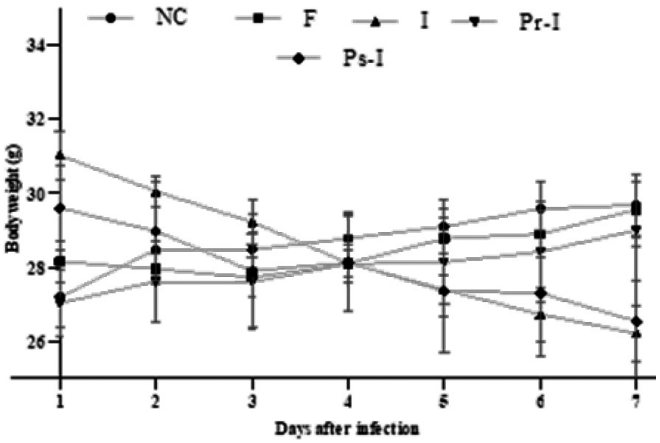

Fig. 2. Weights variation of the five groups of mice during the week following challenge with Salmonella (means±SEM, n=5). NC: Negative control group, I: Infected group, Ps-I: Post-infected group, F: Feeding group, Pr-I: Pre-infected group.

had significantly decreased body weights compared to those at the beginning of pathogen inoculation. This weight loss was attributed to diarrhea occurring on day 3 (Fig. 3), with one death recorded after 6 days of infection. These findings reinforce those of Frizzo *et al*. (2010) and Gill *et al*. (2001). In the Ps-I group, mice lost weight but not significantly. Previous studies have also reported that *Salmonella*-infected mice showed a decrease in body weight (Deriu *et al*., 2013; Kim *et al*., 2013; Kemgang *et al*., 2016; Gancarčíková *et al*., 2019).

Fig. 3. Faecal consistency in mice. I (infected group): muddy-mucous yellow stool, NC (Negative control group): normal brown formed stool

Counting Salmonella Typhimurium *ATCC 13311*

The feces of mice challenged with *Salmonella* (I, Pr-I, and Ps-I groups) were collected aseptically on days 3 and 7 after infection, and the fecal bacteria were counted. The results obtained (Table 1) show that the growth of pathogenic bacteria was completely inhibited when mice were continuously given probiotic for one week prior to infection (Pr-I group).

This preventive effect may be attributed to the colonization of the intestinal tract by the probiotic bacteria, which could inhibit the proliferation of *Salmonella* by blocking the adhesiveness of pathogens, by producing antibacterial substances and stimulating the host's immune system (Nakazato *et al.*, 2011). In a previous study, two strains of infantile bifidobacteria were shown to exert effective antimicrobial activity against *S.* Typhimurium infection after colonization of C3/He/Oujco axenic male mice (Lievin *et al.*, 2000).

Table 1. Viable cell counts of *Salmonella* Typhimurium 13311 in fecal material of mice.

Groups	Log_{10} CFU/g (Mean±sd)	
	3 days	7 days
Infected	5.45±0.50	7.045±0.07
Pre- infected	Nd	Nd
Post- infected	Nd	5.735±0.07

Data are means ±SD from three replications.
Nd: Not determined

Kim *et al*. (2013) found that when rats were gavaged with 5×10^{10} CFU/ml of *S.* Typhimurium, the two live probiotic groups studied had discharge rates of 24% and 13.2% of *Salmonella*, respectively. The anti-*Salmonella* effect was also demonstrated in mice fed with combined probiotic LAB strains isolated from fermented Ethiopian food. Thus, the number of fecal *Salmonella* Typhimurium DT104 cells was significantly reduced from 2.30 to 0.00 Log_{10} CFU/ml compared to the *Salmonella* infected group (Mulaw *et al*., 2020).

Nevertheless, another study showed that *Lactobacillus* and *Pediococcus* strains did not offer any protection against *Salmonella* infection in mice. This may be related to host specificity, as the probiotic isolates were obtained from poultry (Andino *et al*., 2014).

When the probiotic is given to the mice during the challenge (Ps-I) group, it delays the growth of the pathogen, which is not detected in the fecal samples on the 3rd day post infection. On the contrary, mice without probiotics (I group) showed a high population of *S.* Typhimurium, which reached 7.045 Log_{10} CFU/g on day 7 post-infection.

Histological examination

The histopathological analysis of ileum sections (Fig. 4) from the Pr-I and F groups showed that their villi architecture was preserved compared with that of the NC group. While the villi in the Ps-I group demonstrated minimal atrophy. In the I group, *S.* Typhimurium caused intestinal inflammation characterized by edema and significant damage

to the structure of the villi with a diffuse inflammatory infiltrate.

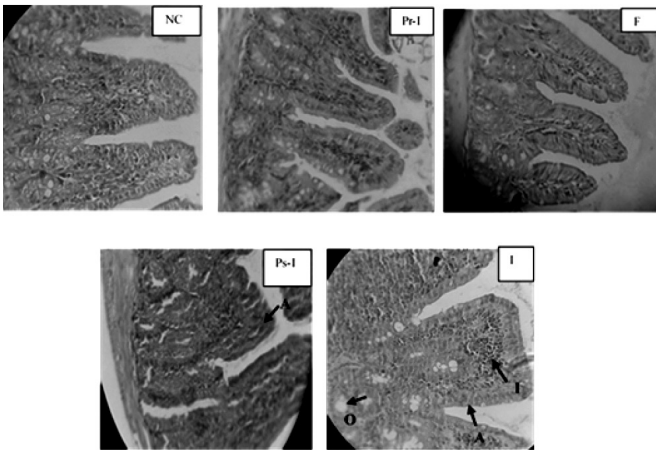

Fig. 4. Representative histological images of haematoxylin and eosin stained of ileum sections. NC: Negative control group, I: Infected group, Ps-I: Post-infected group, F: Feeding group, Pr-I: Pre-infected group. A: villi atrophy, O: oedema, I: Inflammatory infiltrate

Compared with the NC group, liver sections in the F group retained their normal architecture (Fig. 5). Localized vascular congestion was observed in some sections of the Pr-I group. However, diffuse vascular congestion appeared in the liver sections of the Ps-I group. Moreover, in the infected group, diffuse congestion of portal and centrilobular veins was observed with an inflammatory infiltrate in some sites.

Typically, in a murine model, *S.* Typhimurium translocates through the intestine and becomes systemic, infecting many organs **(**Gancarčíková *et al*., 2019). In the infected group, it is noticeable that the *Salmonella* infection damaged the ileum and the liver. This is due to the colonization of pathogenic bacteria in the intestines, which explains the high bacterial level in the feces and the onset of mucous diarrhea on day 3 post-infection. The pathogenic bacteria migrated systemically to the liver, where they multiplied in the liver tissue and damaged it with the recording of a single dead mouse on day 6 of the infection.

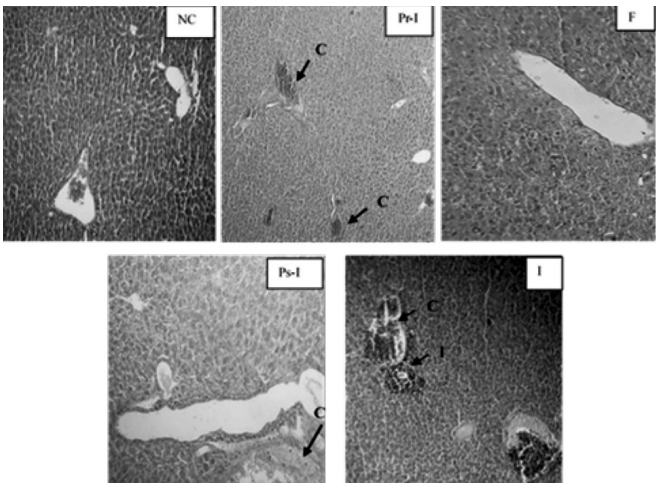

Fig. 5. Representative histological images of haematoxylin and eosin stained of liver sections. NC: Negative control group, I: Infected group, Ps-I: Post-infected group, F: Feeding group, Pr-I: Pre-infected group.C: Congestion, I: Peritorial inflammatory infiltrate

Regarding the Ps-I group, administering mice with the probiotic after the challenge with *Salmonella* did not offer good protection of the ileum and the liver tissue. This is correlated with the fecal load of *Salmonella* and the general health status of mice.

Nevertheless, in the Pr-I group, the probiotic bacteria prevented the infection of the ileum, but in some mice, localized congestion was observed in their livers. This result is in accordance with that of Rishi *et al*. (2009), who reported that the use of probiotics, prebiotics, and synbiotics reduced bacterial translocation to the liver in mice infected with *S.* Typhimurium, and consequently, the damage was minimized compared to that suffered by the unsupplemented mice. In addition, it was found that the combination of LAB strains used in a subsequent study significantly reduced the number of viable *Salmonella* cells in the liver and spleen of mice (Tsai *et al*., 2011). Feeding *L. mesenteroides* strain P45 for 7 days has been reported to reduce infection of the liver and spleen, which may enhance the host immune response by reducing the impact of infection (Giles-Gómez *et al.*, 2016).

It was also found that when the mice were fed the probiotic, it did not cause any histological changes in the ileum or the liver, which both appeared normal. As well as the general health status of the mice treated with the probiotic, these results indicated that the use of this strain is apparently safe. Similar results were obtained by other probiotic LAB in previous studies performed in mouse or chick models (Steinberg *et al*., 2014; Shao *et al*., 2022).

Conclusion

This research indicates that *L. mesenteroides* LK-151 isolated from fermented camel milk appears to be safe and possesses *in vivo* probiotic potential. It also has a remarkable preventive effect, lowering the harmful effects of *S.* Typhimurium infection. However, administration of the probiotic during the infection did not appear to have a therapeutic effect.

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