ORIGINAL ARTICLE

The Effectiveness of *Lactobacillus rhamnosus* Administration on the Growth of *Klebsiella pneumoniae* in Mice (*Mus musculus*)

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ABSTRACT

Introduction: *Klebsiella pneumoniae* is a bacterium from the Enterobacteriaceae family and is considered one of the most dangerous pathogens. Antibiotics are crucial for treating acute bacterial infections. Using probiotics has become one of the supportive and curative efforts in managing the growth of *K. pneumoniae*. One probiotic derived from microorganisms is *Lactobacillus rhamnosus*. This study aimed to determine the effectiveness of *L. rhamnosus* on the growth of *K. pneumoniae* in mice (*Mus musculus*).
Methods: This was an experimental post-test study. The study population consisted of mice aged 3 to 4 months, weighing 20 to 40 grams, determined using Federer's formula. Mice were given standard feed and sterile distilled water. A total of 30 mice were tested and divided into five treatment groups. The distribution colony count test was used for evaluation.
Results: Among the five groups studied, probiotic intervention in the group receiving a combination of *L. rhamnosus* and the antibiotic ceftriaxone showed effective results ($p<0.05$), as did the group given only the probiotic *L. rhamnosus* ($p<0.05$). In contrast, the other groups did not show effective results ($p>0.05$).
Conclusion: The administration of *L. rhamnosus* is effective as a supportive and curative treatment, but it is not effective as a preventive measure against the growth of *K. pneumoniae* in mice.

INTRODUCTION

Klebsiella pneumoniae is a bacterium from the Enterobacteriaceae family and is considered one of the most dangerous pathogens. It is a significant infectious agent because it can cause various diseases and increase antibiotic resistance.[1] *Klebsiella* species are classified as opportunistic pathogens that can cause life-threatening infections such as pneumonia, urinary tract infections, bloodstream infections, and sepsis. These bacteria are of particular concern for neonates, the elderly, and immunocompromised individuals, including healthcare workers.[2]

Based on data from the World Health Organization (WHO), *K. pneumoniae* has been reviewed and listed as a critical priority for developing new antibiotics.[3] In the United States (US), pneumonia has been reported as the sixth leading cause of death and the primary cause of death due to infections.[4] A previous study indicated that 2.1% of pneumonia-causing pathogens were due to bacteria producing extended-spectrum β-lactamases (ESBL), with the highest prevalence originating from *K. pneumoniae* isolates.[5] The prevalence of pneumonia infections among adults in

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Indonesia was reported at 4% in 2018, based on diagnoses by healthcare workers.[6] The highest regional prevalence was reported in Nusa Tenggara (11%), while Bali reported a significant prevalence of 3%.[6] Furthermore, a study conducted in several regional hospitals in South Sulawesi revealed that nearly 30% of patients were identified as positive for *K. pneumoniae* cultures.[7]

Antibiotics are crucial for treating acute bacterial infections. However, the overuse or misuse of antibiotics in humans, livestock, and other applications has led to the emergence of numerous drug-resistant organisms or multidrug-resistant (MDR) organisms.[8] A previous study showed that some *K. pneumoniae* clones exhibit virulent traits, resistance to multiple drugs, and antimicrobial resistance at the cellular level.[2]

According to a global WHO survey, the spread of *K. pneumoniae* is a serious concern due to its resistance to penicillin, cephalosporins, carbapenems, and aztreonam caused by O and K antigens.[9] Both of these antigens can enhance the bacterium's pathogenicity, resulting in fewer options for effective therapy.[9] This situation has driven researchers to explore alternative antimicrobial therapies as antibiotic substitutes. One such alternative involves using beneficial microorganisms, specifically probiotics, to eliminate potential pathogens and restore microbial balance.[10]

Probiotics have been utilized as both a supportive and curative approach in controlling the growth of *K. pneumoniae*. This is due to probiotic species' ability and antimicrobial properties, which help suppress the growth of pathogenic bacteria such as *K. pneumoniae*. One probiotic derived from microorganisms is the bacterium *Lactobacillus rhamnosus*. It is a gram-positive bacterium and one of the most commonly used probiotics. It possesses beneficial properties for biological therapy and plays a role in immunomodulatory functions.[11,12] Therefore, this study aimed to determine the effectiveness of *L. rhamnosus* on the growth of *K. pneumoniae* in mice (*Mus musculus*).

METHODS

This experimental post-test study was conducted in May 2024 at the Laboratory of Microbiology Research, Faculty of Medicine, Universitas Hasanuddin, Makassar. This study was approved by the Ethics Committee of the Faculty of Medicine of Universitas Muslim Indonesia, Makassar. In this study, the independent variable was *L. rhamnosus*, and the dependent variable was the growth culture of *K. pneumoniae* in mice.

Study Population

The mice used in this study were BALB/c strain mice obtained from the Laboratory of Microbiology Research, Faculty of Medicine, Universitas Hasanuddin, Makassar. The study population consisted of mice aged 3 to 4 months and weighing 20 to 40 grams. A total of 30 mice were used as samples, divided into five experimental groups, each consisting of six mice.

Preparation of Bacteria and Probiotics

a. Culture media preparation

The culture media were prepared using nutrient agar (NA). 2.3 grams of NA were dissolved in 100 mL of distilled water and stirred on a hot plate until completely dissolved. The media were sterilized in an autoclave at 121°C for 15 minutes.

b. Bacteria rejuvenation

The rejuvenation of *K. pneumoniae* isolates was performed using slanted NA media. A single bacterial loop from the stock was streaked on the slanted NA media. The culture was incubated at 37°C for 24 hours. This bacterial isolate was administered to the model animals (mice) as an infectious agent.

c. Suspension preparation

The rejuvenated bacteria were harvested and suspended by placing them in a tube containing 5 mL of sterile physiological NaCl. The prepared bacterial suspension was standardized to match the turbidity of McFarland standard 0.5. The suspension was adjusted to 10^6 CFU/mL for *K. pneumoniae* and 10^7 CFU/mL for *L. rhamnosus*.

Procedure

a. Treatment group

The treatment phase began with an adaptation stage, during which the mice adjusted to their environment to ensure they were not stressed during the intervention phase due to relocation from their previous cages. This adaptation phase lasted for 7 days in the laboratory, followed by the respective treatments:

- **Treatment group 1:** The preventive group, where mice were administered *L. rhamnosus* orally at a dose of 10^7 CFU/mL for 3 days. The mice were then inoculated with *K. pneumoniae* at a dose of 10^6 CFU/mL intraperitoneally, 24 hours before blood sampling.
- **Treatment group 2:** The curative group, where mice were inoculated with *K. pneumoniae* at a dose of 10^6 CFU/mL intraperitoneally. Twenty-four hours post-infection, the mice were given *L. rhamnosus* at a dose of 10^7 CFU/mL orally for 3 days, followed by blood sampling on the fourth day.

- **Treatment group 3:** The supportive group, where mice were inoculated with *K. pneumoniae* at a dose of 10^6 CFU/mL intraperitoneally. Twenty-four hours post-infection, the mice were treated with ceftriaxone at a dose of 0.0026/20 g of body weight intraperitoneally, combined with *L. rhamnosus* at a dose of 10^7 CFU/mL orally for 3 days, followed by blood sampling on the fourth day.
- **Treatment group 4:** The positive control group, where mice were inoculated with *K. pneumoniae* at a dose of 10^6 CFU/mL intraperitoneally. Twenty-four hours post-infection, the mice were treated with ceftriaxone at a dose of 0.0026/20 g of body weight intraperitoneally for 3 days, followed by blood sampling on the fourth day.
- **Treatment group 5:** The negative control group, where the mice were inoculated with *K. pneumoniae* at a dose of 10^6 CFU/mL intraperitoneally. Twenty-four hours post-infection, the mice were administered aquadest without further intervention for 3 days, followed by blood sampling on the fourth day.

b. Suspension preparation

Blood samples were collected from the test animals 24 hours after treatment. The mice were anesthetized via intraperitoneal injection of ketamine/xylazine (100/10 mg/kg) and sacrificed through intracardiac exsanguination. Blood samples were drawn from the heart and placed in Ethylenediaminetetraacetic acid (EDTA) tubes. The collected blood (0.1 mL) was enriched in brain-heart infusion broth medium and observed for 3 days while being compared to turbidity standards. After enrichment, 0.1 mL of the medium was pipetted at a 10^{-2} dilution level, cultured on MacConkey agar, and then incubated at 37°C for 24 hours. The resulting colonies were counted using a colony counter.

Analytical Methods

The data were obtained by recording the bacterial levels identified in blood samples cultured with *K. pneumoniae* after treatment with *L. rhamnosus*. The data from the treatment groups (1, 2, 3, 4, and 5) were objectively interpreted. Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 16 for Windows and Microsoft Excel, employing the Kruskal-Wallis non-parametric test and the Mann-Whitney test method.

RESULTS

This study focused on the effectiveness of *L. rhamnosus* as a probiotic against the growth of *K. pneumoniae*. The dependent variable studied was the culture growth of *K. pneumoniae*. Data were collected by examining blood samples from mice, which were stored in petri dishes for identification and bacterial counting. The results are presented in tables accompanied by explanations as follows:

Table 1. Distribution of *Klebsiella pneumoniae* bacterial colony count

Variable	Mice 1	Mice 2	Mice 3	Mice 4	Mice 5	Mice 6	Mean
Group 1 (prevention)	15	5	0	1	5	4	5.00
Group 2 (curative)	6	0	5	2	0	2	2.5
Group 3 (supportive)	1	6	1	0	0	0	1.33
Group 4 (control +)	0	0	0	0	0	1	0.16
Group 5 (control -)	5	20	3	15	10	10	10.50

Table 1 shows the distribution of *K. pneumoniae* bacterial colonies. The mean bacterial colony count for the preventive group was 5.00. This group was injected with *L. rhamnosus* first. The group injected K. pneumoniae, including the curative group, had a mean of 2.50; the supportive group had a mean of 1.33; the positive control group had a mean of 0.16; and the negative control group had a mean of 10.50.

Table 2 and 3 present the normality test results and the Kruskal-Wallis H test on the population data. Since the data did not follow a normal distribution, the results were analyzed using the non-parametric Kruskal-Wallis and Mann-Whitney tests. In the Kruskal-Wallis H test, a p-value of 0.004 ($p<0.05$) was obtained, indicating a significant difference among treatment group 1, 2, 3, 4, and 5.

Table 2. Normality test

Group	Kolmogorov-Smirnov	Shapiro-Wilk
	Sig.	Sig.
Group 1 (prevention)	0.036	0.107
Group 2 (curative)	0.200*	0.264
Group 3 (supportive)	0.005	0.002
Group 4 (control +)	0.000	0.000
Group 5 (control -)	0.200*	0.785

*abnormally distributed

Table 3. Kruskal-Wallis H test

	Colony
Kruskal-Wallis H	15.144
df	4
Asymp. Sig.	0.004

df: degrees of freedom; Asymp. Sig.: asymptotic significance

Table 4. Mann-Whitney test

	Comparing	p-value
Group	1:2	0.515
	1:3	0.162
	1:4	0.016
	1:5	0.124
	2:3	0.358
	2:4	0.059
	2:5	0.019*
	3:4	0.211
	3:5	0.01*

*significant

Table 4 shows the effectiveness of *L. rhamnosus* in inhibiting the growth of *K. pneumoniae*. If the significance p<0.05, the hypothesis is accepted, showing a difference in the average colony count. If the significance p>0.05, the hypothesis is rejected.

Table 5. Colony count results comparison

Comparison	Results
Group 1	Preventive showed there was no significant relation (p=0.124) in *Lactobacillus rhamnosus* treatment
Group 2	Curative showed there was a significant relation (p=0.019) in *L. rhamnosus* treatment
Group 3	Supportive also showed there was a significant relation (p=0.01) in *L. rhamnosus* treatment

This indicates that the results of this study demonstrate that the administration of the probiotic *L. rhamnosus* in group 2 (curative) and 3 (supportive) is more effective than in group 1 (preventive).

DISCUSSION

The results indicate that mice in the preventive group (group 1) showed an insignificant result, with a p-value of 0.124 for administering *L. rhamnosus* before injecting *K. pneumoniae* bacteria. The effectiveness of *L. rhamnosus* in preventing *K. pneumoniae* infections appears to be limited, as demonstrated by various studies. Although some studies have shown that *Lactobacillus* strains can exhibit antagonistic activity against *K. pneumoniae*, the overall clinical significance of *L. rhamnosus* remains debatable. Mandal and Hardel (2018) reported that *Lactobacillus* (including *L. rhamnosus*) plays an important role (p<0.05) in protecting hosts against MDR *K. pneumoniae* infections.[13] However, Steele (2022) showed that *L. rhamnosus* administration did not prevent pneumonia in critically ill patients.[14]

The results also indicate that mice in the curative group (group 2) demonstrated significant results (p=0.019) for administration of *L. rhamnosus* after injection with K. pneumoniae colonies. These findings align with a previous study, which showed that *L. rhamnosus* GG filtrate expressed high inhibition percentages against gram-positive, MDR bacteria under the influence of active biological substances from probiotic microorganisms.[15] A 5-hour incubation of test isolates with *Lactobacillus* samples resulted in inhibition rates of 85.6%-96.7% and 100% after 24 hours of exposure.[15]

The results indicate that mice in the supportive group (group 3) exhibited the most significant test results (p=0.001) for administering *L. rhamnosus* combined with an antibiotic after being injected with *K. pneumoniae* colonies. A previous study also investigated the effects of combining *L. rhamnosus* with antibiotics in a different sample.[12] It highlighted the importance of adjuvant therapy using probiotics (*L. rhamnosus GR-1* and *Lactobacillus reuteri RC-14*) combined with a single dose of 150-mg fluconazole during 4 weeks of therapy for vulvovaginal candidiasis.[12] The study found that combining probiotics, such as *Lactobacillus sp.*, with antibiotics enhanced treatment efficacy against *K. pneumoniae* strains.[12] The synergistic effect can help reduce the required antibiotic dosage and minimize the potential side effects of higher doses. The antimicrobial properties of *Lactobacillus sp.* are attributed to their ability to produce lactic acid and other metabolites that inhibit the growth of pathogenic bacteria, such as *K. pneumoniae*. This mechanism is particularly beneficial in situations where antibiotic resistance is prevalent.

Another study also mentioned that the mechanism of action of *Lactobacillus sp.* in inhibiting *K. pneumoniae* involves the production of lactic acid.[16] The ability of *L. rhamnosus* to produce lactic acid and lactate iron inhibits *K. pneumoniae*. Through its probiotic properties, this bacterium can act as a broad-spectrum antibiotic. Another compound, such as hydrogen peroxide, can lower the environmental pH, thereby inhibiting the growth of *K. pneumoniae*. Moreover, the resistance-reducing mechanism is related to acute inflammation involving cytokines such as interferon-γ (IFN-γ), interleukin-17 (IL-17), and tumor necrosis factor-α (TNF-α), which play a crucial role in combating *K. pneumoniae* infections. Disruption or deficiency in the production of these cytokines reduces resistance to infection. If *L. rhamnosus* is not sufficiently effective in stimulating or modulating these signaling pathways, its ability to protect against *K. pneumoniae* infections becomes limited. Studies also indicate that activating neutrophils and C-C chemokine receptor 2-positive ($CCR2^+$) monocytes is critical for protection against infections.[16,17] If *L. rhamnosus* cannot significantly contribute to the activation of these immune cells, its protective effects will diminish.[16,17]

Although *L. rhamnosus* offers some benefits, it may not be potent enough to prevent acute *K. pneumoniae* infections, especially when more complex

and robust immune mechanisms are required to combat the pathogen. In addition, bacteriocin activity produced through ribosomal synthesis plays a supporting role. Bacteriocins are potent antimicrobial peptides that disrupt cell wall and membrane integrity and suppress gene expression. Certain bacteriocins, such as nisin, complement antibiotics and lysozymes and form pores in bacterial membranes by interacting with lipids, leading to membrane potential loss, intracellular metabolite leakage, and bacterial death.[18]

Beyond reducing inflammatory cells and cytokines, a previous study showed that oral administration of *L. rhamnosus* can increase regulatory cytokine levels, such as IL-10 and IL-27, in bronchoalveolar lavage fluid infected with pneumococcal strains.[16] The therapeutic potential of *L. rhamnosus* supports this study by showing that probiotics have good effects on viruses and gram-positive respiratory pathogens by modifying levels of regulatory cytokines, such as IL-10 and/or IL-27. These findings suggest that the ability of probiotic microorganisms to manage harmful inflammation caused by *K. pneumoniae* infection could be a key feature in enhancing resistance to the pathogen. The immunopathological effects of respiratory pathogens, such as *K. pneumoniae*, have been demonstrated to be inhibited by IL-10, especially during the resolution phase of inflammation.[16]

Table 6. Potential inhibition of *Lactobacillus sp.* against *Klebsiella pneumoniae* virulence factors

Virulence Factors of *K. pneumoniae*	Potential of *Lactobacillus* sp.
Polysaccharide capsule[19]	Production of bacteriocins and organic acids that weaken the capsule[20]
Biofilm[19]	Inhibition and disruption of biofilm formation[21]
Antibiotic resistance[8]	Natural antimicrobial production to counter resistance[8]
Host cell adhesion[22]	Binding to adhesion receptors[22]
Immune system modulation[22]	Activation of immune cells and enhancement of epithelial cell barriers[22]

There is evidence that probiotics can be crucial in treating and preventing infectious diseases. Currently, infectious diseases are generally managed with antibiotics. However, the overuse of antibiotics can result in adverse medication reactions for individual patients, as well as public health problems, including the selection of bacteria that are resistant to many drugs. Thus, there is an urgent need to find innovative antimicrobial therapy options, focusing on natural product-based treatments.[23]

CONCLUSION

The administration of *L. rhamnosus* is effective as a curative measure against the growth of *K. pneumoniae*. Additionally, it proved effective as a supportive treatment against the growth of *K. pneumoniae* in mice. However, it is ineffective as a preventive measure against the growth of *K. pneumoniae* in mice.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Conceived and designed the study, collected, analyzed, interpreted the data, and wrote the manuscript: IFA. Offered guidance, contributing to substantial intellectual content during the drafting process, and revising the manuscript: EPW, DA, RPLB, YS, NN. All authors contributed and approved the final version of the manuscript.

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