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Antibiotic Susceptibility Profiles and Potential of Lactic Acid Bacteria from *Dadih* as Antimicrobial Producers and *Dangke* Whey Fermenters

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ABSTRACT

We aimed to explore the potential of lactic acid bacteria (LAB) indigenous *Dadih* (Indonesian traditional fermented buffalo milk) as antimicrobial producers and to see their ability as *Dangke* whey fermenters. Nine isolates belonging to *Lactobacillus plantarum* (designed as LP007, LP021, and LP050), *Lacticaseibacillus paracasei* (LC028, LC039, and LC040), and *Levilactobacillus brevis* (LB025, LB042, and LB055) were used in this study. Antagonistic activity was performed to evaluate the antimicrobial activity in inhibiting *Escherichia coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* from ATCC strain and field-resistant strains. The susceptibility test was conducted to evaluate the LAB sensitivity profile to sixteen antimicrobials. Furthermore, the potential of *L. plantarum*, *L. paracasei*, and *L. brevis* was observed to see their ability as *Dangke* whey fermenters (a byproduct from Indonesian traditional cheese). The results showed that LAB isolates are generally greater in inhibiting Gram-negative than Gram-positive bacteria. Particularly, *L. plantarum* showed strong activity against ATCC strains and intermediate-strong level to antibiotic field-resistant strains. Nevertheless, all strains showed the ability to produce antimicrobial products. Our results also showed that *L. plantarum* LP007 revealed the lowest resistance profile as a potential probiotic. In addition, *L. plantarum*, *L. paracasei*, and *L. brevis* could ferment *Dangke* whey at 37°C in 24-48 h incubation. In conclusion, studied LAB isolates showed ability as antimicrobial producers, and this study presents the variety of LAB species that can be used as *Dangke* whey starters.

Key words: Antimicrobial, *Dadih*, *Dangke* whey, Lactic acid bacteria

INTRODUCTION

Resistance to antibiotics is a major health problem in both human and veterinary medicine. Recently, some studies have shown that resistance to critically important antimicrobials listed by the World Health Organization (www.who.int) has emerged worldwide, such as resistance to third-generation cephalosporins, new quinolones, and high-level aminoglycosides (Rajendiran et al. 2022; Islam et al. 2023). This situation will result in a significant impact on healthcare settings due to the limited therapy for serious infections (Salam et al. 2023; Barmpouni et al. 2023). Nevertheless, some microorganisms can produce secondary metabolites that have the ability to combat resistant pathogens (Devi et al. 2023; Rusu et al. 2023). Lactic acid bacteria (LAB) are known as major probiotic microorganisms that produce bacteriocins as antimicrobial compounds (Yuliana et al. 2020). Besides that, LAB also produce antimicrobial properties such as lactic and acetic acids, hydrogen peroxide, or diacetyl (Kralik et al. 2018). The use of probiotics is a natural alternative for the prevention and treatment of many diseases (Żukiewicz-Sobczak et al. 2014; Tegegne and Kebede 2022). At the end of 2018, it was estimated that the probiotics market reached US$ 6,762.2 million and is predicted to continue to increase in the future (Zielińska and Kolożyn-Krajewska 2018).

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Indonesia has various traditional fermented foods, such as *Dadih*, which is yogurt made from buffalo milk. *Dadih*, a traditional fermented milk product from West Sumatra, Indonesia, is known for its distinct taste and texture. Its unique sensory characteristics are attributed to the fermentation process driven by LAB (Surono 2015). *Dadih* has been reported to contain LAB such as *Lactobacillus pentosus*, *L. plantarum*, and *Lactococcus lactis* (Wirawati et al. 2019). Lactic acid bacteria in *Dadih* were also reported to have health-beneficial properties such as antimicrobial, hypocholesterolemic, antimutagenic, antioxidant, immunomodulatory, gamma-aminobutyric acid (GABA), and folate-source (Arnold et al. 2021). Bioprospecting these indigenous LAB holds promise for various applications. On the other hand, Indonesia also has traditional cheese made from buffalo or cow milk from Enrekang Regency, South Sulawesi Province, named *Dangke*. Nevertheless, *Dangke* production resulting whey as a byproduct, which is usually wasted to the environment (Syah et al. 2017). In this study, we evaluated the potential of LAB indigenous *Dadih* as antimicrobial producers and its potential to be used as *Dangke* whey starters.

MATERIALS AND METHODS

Lactic acid bacteria

In this study, we used nine strains of lactic acid bacteria belonging to *Lactobacillus plantarum* (designed as LP007, LP021, and LP050), *Lacticaseibacillus paracasei* (LC028, LC039, and LC040), and *Levilactobacillus brevis* (LB025, LB042, and LB055) as Dr. Sri Rahmatul Laila's isolate collections at the School of Veterinary Medicine and Biomedical Science, IPB University. Previously, those isolates were collected from *Dadih* and identified to the species using MALDI-TOF MS (Bruker, MA, US) (Laila et al. 2024). We only selected the isolates with the high-confidence score value ranging from 2.00 to 3.00 based on MALDI-TOF MS results.

Antagonistic activity

The ability of antimicrobial activity produced by LAB isolates were evaluated with minor modification of agar overlay method as Halder et al. (2017). Each isolate was cultured into de Man, Rogosa and Sharpe (MRS) broth (Oxoid; CM0359B; USA) and incubated at 37°C for 48h. Then, a full loop (~10µl) of each strain was spotted onto MRS agar (Oxoid; CM0361; USA) and incubated at 37°C for 48h. Culture isolates were overlaid with soft Luria-Bertani agar (LB broth (LENNOX) (Oxoid; L3022-250G; USA) mixed with 0.8% agar (BD Difco™; 3242810; USA) pre-mixed with 10^8 colonies forming unit (CFU) of the challenge strains (one on each MRS agar plate) and incubated after solidification of the overlaid agar medium, at 37°C for 24h. The challenge strains that were used in this study consisted of *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, and *Staphylococcus aureus*, ATCC 29213. In this experiment, we also used antibiotics field-resistant isolate collections from the Laboratory of Veterinary Public Health, IPB University, including *E. coli* 18 (resistant to Cefotaxime, Trimethoprim-Sulphamethoxazole, Nalidixid Acid, Gentamicin, Azithromycin, Nitrofurantoin, and Fosfomycin), and *E. faecalis* 59 (resistant to Ciprofloxacin, Tetracyclin, Teicoplanin, Vancomycin, and Erythromycin) isolated from raw milk, and *S. aureus* 63 (resistant to Linezolid, Chloramphenicol, Erythromycin, Ceftaroline, and Cefoxitin) isolated from *Dadih.* The zone diameter of inhibition (ZDI) was determined as the difference between the inhibition zone and the spotted culture zone (ø mm). Then, the result was interpreted based on ZDI form on the MRS-LB agar plate with criteria strong, intermediate, and weak inhibition (>20mm, 10–20mm, and <10mm, respectively). The tests were conducted in triplicate.

On the other hand, we also observed the antimicrobial activity from the supernatant of LAB cultures. After 48h incubation, the supernatant and pallet from the cultures were separated. Then, half of the supernatant was heated at 95°C for 10min. 10µl of each supernatant with/without heating was applied to a 6mm blank filtered disc, and the inhibition activity was tested to four ATCC strains on the LB agar plate and incubated at 37°C for 24h.

Antibiotic susceptibility

Antimicrobial susceptibility assays were performed to evaluate the nine LAB isolates to 16 antibiotic agents by the Kirby-Bauer method. Antimicrobial susceptibility assays to *Lactobacilli* bacteria still don't have definitive standards to interpret the result from the Clinical and Laboratory Standards Institute CLSI. So, in this study, the results were compared and interpreted based on Sharma et al. (2017). The antibiotics that were used in this study consisted of Penicillin (P 10), Amoxicillin (AML 25), Cefoxitin (FOX 30), Cefotaxime (CTX 30), Vancomycin (VA 30), Nalidixic acid (NA 30), Ciprofloxacin (CIP 5), Levofloxacin (LEV 5), Gentamicin (CN 10), Tetracycline (TE 30), Doxycycline (DO 30), Erythromycin (E 15), Nitrofurantoin (F 300), Trimethoprim-sulfamethoxazole (STX 25) and Azithromycin (AZM 15) from Oxoid Ltd., and Cefpodoxime+clavulanic acid (PXL 11) from Riverside Medical Supplies Ltd. As a control strain, we used *E. coli* ATCC 25922 in this assay.

Dangke whey fermentation

Dangke whey

Dangke whey was traditionally made based on local people (Enrekang Regency, South Sulawesi Province, Indonesia) to produce *Dangke* products. In this study, we used commercial pasteurized milk as a *Dangke* source with a composition of 8.4% non-fat milk solid and 3.6% milk fat content. Immature papaya fruit sap was prepared and diluted with sterilized water. Milk sample was heated (up to 60°C) and stirred and dropped with diluted papaya sap until crud and whey were separated (Malaka et al. 2017). Then, the *Dangke* whey was refrigerated stock overnight for further work.

Dangke whey fermentation

Dangke whey was sterilized at 115°C for 15 minutes and then cooled to room temperature. Whey fermentation was conducted based on minor modifications from Maruddin et al. (2019). In this study, we used a representative strain from each species as *Dangke* whey fermenters, including *L. plantarum* LP007, *L. paracasei* LC028, and *L. brevis* LB025. Each strain was prepared as a starter for 10^8 CFU/mL, then washed and thereafter resuspended with sterilized distilled water. A 3% volume of the starter was inoculated to *Dangke* whey and incubated at 37°C for 24-48 h. Sterilized distilled water was used as a negative control. The ability of those strains as fermenters was considered when *Dangke* whey pH was reached for 4.0±0.2. In addition, the LAB from *Dangke* whey was enumerated with MRS agar.

Statistical analysis

Statistical analysis was descriptively performed by the Kruskal-Wallis test if the normal distribution of ZDI was not met by Shapiro-Wilk's test using R software (Version 1.2.5033) to show the significance of ZDI between tested species. Then, the Wilcoxon test was conducted to determine if the results of a Kruskal-Wallis test were statistically significant to determine which groups are different in ZDI between LAB species. The significant difference is indicated with $P<0.05$ or <0.01.

RESULTS

This study investigated the potential of LAB isolated from *Dadih* as antimicrobial producers and *Dangke* whey fermenters. The results showed that LAB isolates displayed greater inhibitory activity against Gram-negative bacteria than Gram-positive ATCC strains, and all LAB showed strong activity in inhibiting *P. aeruginosa* ATCC 27853, as shown in Table 1. Fig. 1 represents the antagonistic assay in this study. No significant difference was observed in inhibition activity between strains in each species against all challenged strains. Nearly all *L. plantarum* strains showed strong activity in inhibiting ATCC strains and tended to have higher activity against Gram-negative bacteria (*E. coli* and *P. aeruginosa*) than Gram-positive bacteria (*S. aureus* and *E. faecalis*).

Beyond the strong overall activity observed in *L. plantarum* isolates, our findings revealed some variation in antimicrobial activity among the other LAB species. *L. paracasei* isolates showed strong and intermediate activity in inhibiting Gram-negative and Gram-positive bacteria, respectively. On the other hand, *L. brevis* revealed strong, intermediate, and weak activity against *P. aeruginosa*, *E. coli*, and Gram-positive bacteria, respectively. Nevertheless, all supernatants from tested isolates did not show inhibition activity under our laboratory conditions.

After recognizing the antimicrobial activity produced by the collected LAB strains, we tested them against field-type isolates that showed multi-drug antibiotic resistance. On average, LAB isolates could inhibit field-type isolates in intermediate to strong levels (Fig. 2). Interestingly, *L. plantarum* and *L. brevis* showed strong activities, and *L. paracasei* at an intermediate level in inhibiting *E. coli* 18. Furthermore, all species generally showed inhibition activities to *S. aureus* 59 and *E. faecalis* 63 at the intermediate level.

To see the potential of LAB isolates indigenous *Dadih* as probiotic candidates, we further observed the susceptibility profile of those isolates (Table 2). *L. plantarum* LP007 and LP021 revealed susceptibility to β-lactam and cephalosporin antibiotics (Penicillin, Amoxicillin, Cefoxitin, Cefotaxime, and Cefpodoxime+clavulanic acid), and other LAB isolates

Table 1: The average inhibition zone diameter produced by lactic acid bacteria isolated from *Dadih* to tested isolates

Species	Strains	Average of zone diameter of inhibition (mm)						
		P. aeruginosa ATCC 27853	*E. coli* ATCC 25922	*S. aureus* ATCC 29213	*E. faecalis* ATCC 29212	*E. coli* 18	*S. aureus* 63	*E. faecalis* 59
L. plantarum	LP007	36.67	36.67	23.00	23.67	24.90	14.13	14.00
	LP021	36.00	36.00	27.33	21.67	22.17	13.93	9.87
	LP050	36.00	36.00	20.33	20.33	29.33	13.60	12.47
L. paracasei	LC028	36.00	32.00	16.33	16.33	19.83	12.57	10.87
	LC039	36.00	30.67	14.33	13.33	18.90	10.03	9.77
	LC040	36.00	26.67	17.67	19.33	18.13	9.37	10.70
L. brevis	LB025	36.00	13.33	6.33	3.00	24.60	9.57	10.07
	LB042	36.00	13.00	5.33	1.00	23.33	10.70	12.40
	LB055	36.00	9.33	3.33	3.00	23.70	9.00	12.50

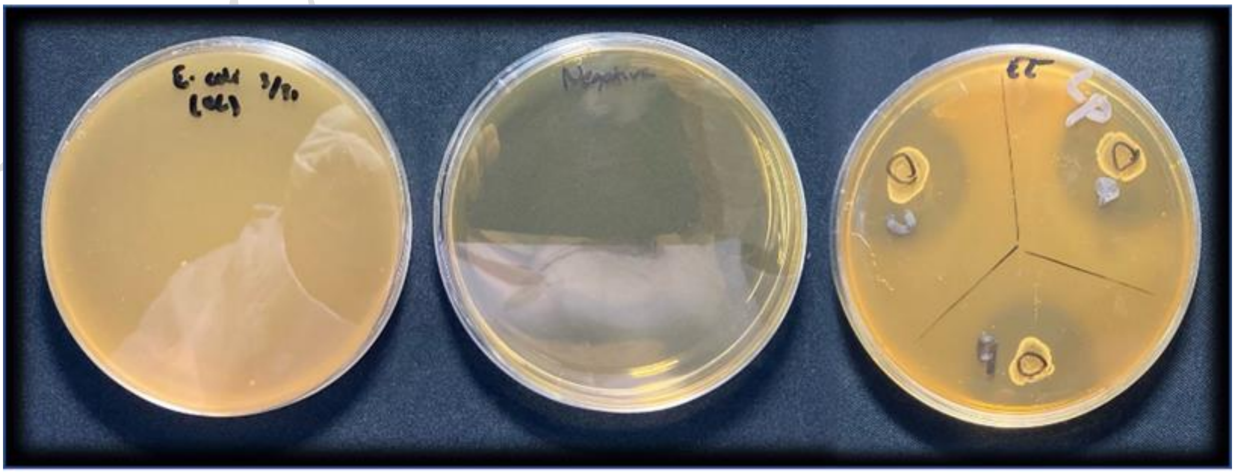

Fig. 1: Antagonistic activity test using the overlay method. The left side shows MRS agar plate overlaid with LB soft agar pre-mixed with *E. coli* 18, the center shows MRS agar plate overlaid with LB soft agar only, and the right side shows MRS agar plate containing spotted cultures of *L. plantarum* overlaid with LB soft agar pre-mixed with *E. coli* 18.

Table 2: Antimicrobial susceptibility profile of lactic acid bacteria indigenous *Dadih* in this study

Antibiotics[1]	*L. plantarum*			*L. paracasei*				*L. brevis*	
	LP007	LP021	LP050	LC028	LC039	LC040	LB025	LB042	LB055
Penicillin	S	S	S	S	S	S	S	S	S
Amoxicillin	S	S	S	S	S	S	S	S	S
Cefoxitin	S	S	R	R	R	I	R	R	R
Cefotaxime	S	S	S	S	S	S	S	S	S
Cefpodoxime+clavulanic acid	S	S	S	S	S	S	S	S	S
Vancomycin	R	R	R	R	R	R	R	R	R
Nalidixic acid	R	R	R	R	R	R	R	R	R
Ciprofloxacin	R	R	R	R	R	R	R	R	R
Levofloxacin	I	R	I	I	S	I	R	R	R
Gentamicin	R	I	R	R	R	R	R	R	R
Tetracycline	S	S	S	S	S	S	S	S	S
Doxycycline	S	I	S	S	S	S	S	S	S
Erythromycin	S	S	S	S	S	S	S	S	S
Nitrofurantoin	S	S	I	S	S	S	I	S	S
Trimethoprim-sulfamethoxazole	S	S	S	S	S	S	S	S	S
Azithromycin	S	S	S	S	S	S	I	I	S

[1]R: resistant, I: intermediate, and S: susceptible.

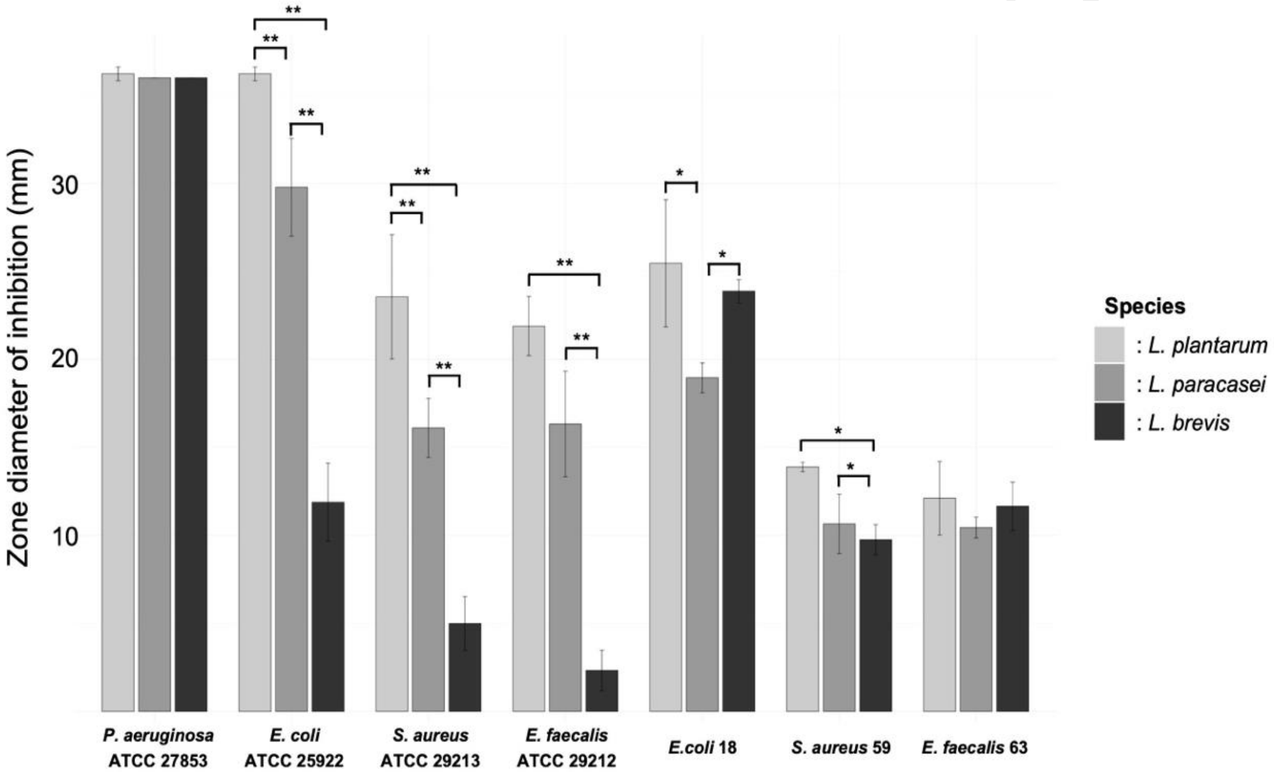

Fig. 2: Comparison of antimicrobial activity of *L. plantarum, L. paracasei*, and *L. brevis* to challenged isolates. Significant differences in the group are indicated with * ($p<0.05$) and ** ($p<0.01$).

revealed non-susceptible to only Cefoxitin derivate. Then, none of LAB isolates revealed resistance to Tetracycline, Doxycycline, Erythromycin, Nitrofurantoin, Trimethoprim-sulfamethoxazole, and Azithromycin. On the other hand, most of LAB isolates revealed resistance to Vancomycin, Nalidixic acid, Ciprofloxacin, Levofloxacin, and Gentamicin.

In this work, we also investigated the potential of *L. plantarum*, *L. paracasei*, and *L. brevis* as *Dangke* whey fermenters. The final fermented *Dangke* whey products resulted in 10^{10} to 10^{11} CFU/mL of LAB at 3.8~4.0 pH, and the products also showed favor as common yogurt. *L. plantarum* LP007 and *L. paracasei* LC028 could ferment *Dangke* in 24 h incubation with 3.98 and 3.94 pH, respectively. *L. brevis* LB025 contained 3.9×10^6 CFU/mL with 5.94 pH at 24h incubation and fermentation was done in 48h incubation with 3.82 pH and containing 2.8×10^{10} CFU/mL of LAB. The *Dangke* whey fermentation process and final product profile are summarized in Table 3 and Fig. 3.

DISCUSSION

This study used three LAB species isolated from *Dadih* to test their potential as antimicrobial producers against *E. coli* and *P. aeruginosa,* which belonged to Gram-negative bacteria, and *S. aureus* and *E. faecalis,* which belonged to Gram-positive bacteria. Those bacteria are commonly found in the environment and human gut as commensal bacteria. Nevertheless, they are also classified as opportunistic pathogens that can cause nosocomial

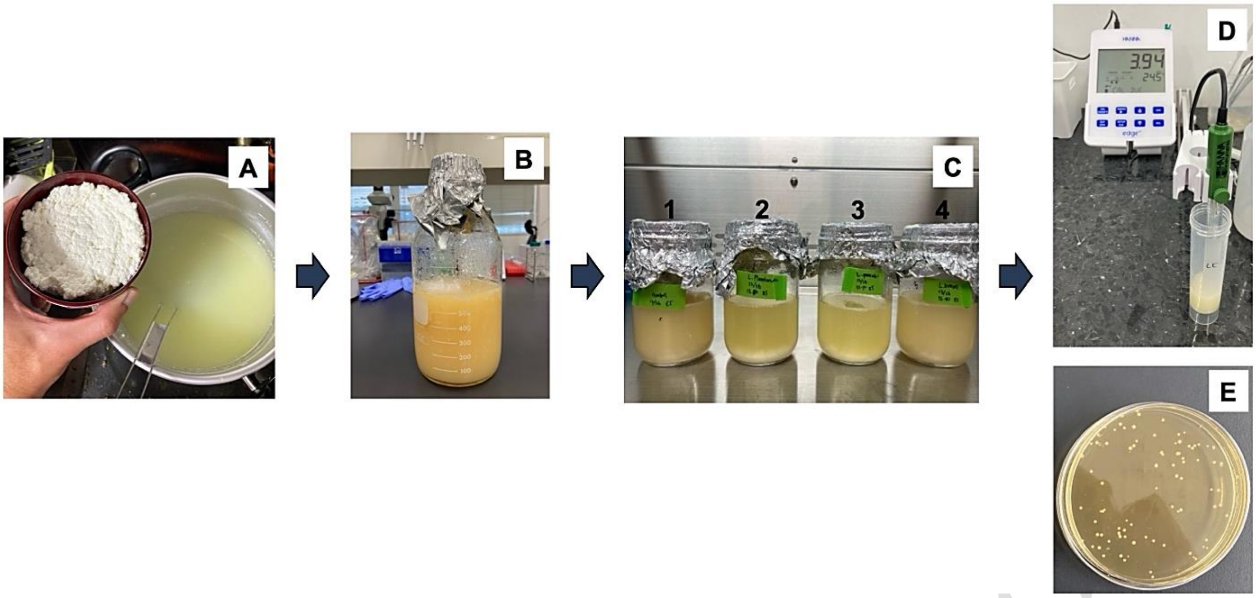

Fig. 3: Fermentation of *Dangke* whey using lactic acid bacteria (LAB) indigenous *Dadih.* A) Preparation of homemade *Dangke* whey, B) Autoclaved *Dangke* whey, C) Unfermented *Dangke* whey (1), fermented *Dangke* whey with *L. plantarum* (2), *L. paracasei* (3), and *L. brevis* (4). Measurement of pH (D) and LAB enumeration (E) from fermented *Dangke* whey.

Table 3: *Dangke* whey profile after fermentation with lactic acid bacteria (LAB) indigenous *Dadih*

Treatment	CFU/mL	pH	Incubation time (Hours)
Before treatment	-	6.15	0
L. plantarum LP007	3.9×10^{10}	3.98	24
L. paracasei LC028.	1.0×10^{11}	3.94	24
L. brevis LB025	2.8×10^{10}	3.82	48
Distilled water	-	6.13	24
Distilled water	-	6.01	48

infection (Ch'ng et al. 2022; Qin et al. 2022; Denissen et al. 2022). Our results suggested that all tested LAB strains have potential antimicrobial activity in inhibiting opportunistic bacteria. This finding aligns with a previous study where plantaricin P1053, a bacteriocin produced by *L. plantarum* PBS067, demonstrated broad-spectrum activity against *E. coli*, *S. aureus*, *P. aeruginosa*, and *E. faecalis* (Ibrahim et al. 2021; Letizia et al. 2022). It is important to consider that no inhibition activity was shown by supernatants from the tested isolates, and it is suggested that their ability depends on the concentration of the produced metabolite substrate. However, further analysis such as treated supernatant from crude extract, must be conducted to obtain sufficient concentration to inhibit challenged isolates (Ren et al. 2018).

In recent studies, cephalosporinase-producing *E. coli* has become a major concern in human and veterinary medicine in Indonesia (Sunarno et al. 2023; Rizal et al. 2024). Furthermore, high contamination of *E. coli* (70.4%; 176/250) and *S. aureus* (55.2%; 138/250) in dairy milk has been reported in the country (Tyasningsih et al. 2022). *E. coli* 18 was recognized as a Cefotaxime-resistant strain isolated from raw milk that could be inhibited by LAB strains with strong levels in this study, suggesting that *E. coli* contamination can be eliminated by LAB indigenous *Dadih* during fermentation. To our knowledge, extended-spectrum β-lactamase-producing *E. coli*, methicillin-resistant *S. aureus* and high-level aminoglycosides-resistant enterococci are reported as the main concerns in human infections (Diab et al. 2019; Samia et al. 2022; Sharifzadeh Peyvasti et al. 2020). Lactic acid bacteria such as *L. plantarum* have been reported to inhibit *E. coli* adhesion to human intestinal cells in vitro (Alizadeh Behbahani et al. 2019). So, our results suggested that *Dadih* consumption could prevent the risk of pathogen infection in the intestine due to LAB indigenous *Dadih* protection and also has antimicrobial properties (Arnold et al. 2021).

All LAB isolates revealed susceptibility to β-lactams, macrolide, and tetracyclines derivates. Our results align with LAB isolated from fermented crud milk samples as Sharma et al. (2017). Even though studied LABs are resistant to quinolones, aminoglycosides, and vancomycin, a previous study reported that most the lactobacilli show intrinsic resistance to those antibiotics, which means it has a minimum risk of horizontally transferring the resistant determinant to other bacteria (Anisimova et al. 2022). This study highlights the importance of determining LAB susceptibility profiles. While LAB are generally considered safe, the presence of antibiotic resistance genes can raise concerns about potential transferability to pathogenic bacteria. Selecting LAB strains with low resistance profiles is crucial, especially if they are intended for probiotic applications.

Finally, we assessed LAB isolates indigenous *Dadih* as starter candidates to ferment *Dangke* whey. As mentioned above, *Dangke* whey, as a byproduct of *Dangke*, is usually wasted to the environment. Previous studies have shown that *L. fermentum* indigenous *Dangke* and *L. plantarum* could be used in *Dangke* whey fermentation (Syah et al. 2017; Maruddin et al. 2019). Our results showed that *Dangke* whey fermentation succeeded with the final pH and LAB CFU numbers that are similar to commercial drinking yogurts, as shown in a previous report (Kang et al. 2019). Our study was limited in confirming studied LAB as probiotics. So, further analysis, such as acid and bile salt survival and the ability to colonize the epithelial intestine, still needs to be conducted. Nevertheless, this is the first study that showed the ability of *L. paracasei* and *L. brevis* to be *Dangke* whey starters.

Conclusion

This study revealed the potential of LAB indigenous isolated from *Dadih* as both antimicrobial producers and *Dangke* whey fermenters. *L. plantarum*, *L. paracasei*, and *L. brevis* showed antibacterial activity, while *L. plantarum* LP007 appeared as a promising candidate. It showed the strongest antimicrobial activity against various bacteria and the lowest resistance profile as a probiotic candidate. Furthermore, this study identified a diverse range of LAB species from *Dadih* that have the ability in *Dangke* whey fermentation. The discovery of starter candidates for fermenting *Dangke* whey will increase the utilization of traditional dairy products in health drinks and minimize the environmental waste associated with *Dangke* processing.

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Conflict of interest: There is no conflict of interest.

Author's Contribution

Conceptualization: ES and SRL. Investigation: ES. Writing – original draft: ES and SRL. Writing – review, and editing: ES, SMN, EM, RW, SW, EK, A, MS, DE, TA, and FR. Data curation and Validation: ES. Project administration and Supervision: ES.

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