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Efficacy of Saccharomyces Boulardii as an Adjunct Therapy in Children with Non-Specific Acute Diarrhea: A Double-Blind Randomized Controlled Trial

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ABSTRACT: In developing nations, non-specific acute diarrhea remains a pediatric illness. Standard treatment may not hasten recovery, indicating a need for effective adjunctive therapies. This study assessed Saccharomyces boulardii for children with non-specific acute diarrhea. A double-blind, randomized, placebo-controlled trial was conducted from November 2025 to January 2026 at three hospitals in Makassar, Indonesia. Sixty children aged 6 months to 5 years were randomized to standard therapy plus S. boulardii (250 mg twice daily for 5 days) or placebo. Primary outcomes were diarrhea frequency and stool consistency. Baseline characteristics were homogeneous ($p > 0.05$). The intervention group showed a significantly faster reduction in diarrhea frequency from Day 2 to Day 5 than controls ($p < 0.05$). Stool consistency also improved faster, with 96.7% achieving solid stool by Day 5 versus 100% remaining soft in controls ($p < 0.001$). Median diarrhea duration was 3 days in both groups ($p = 0.584$). Adjunctive S. boulardii accelerated daily improvement without shortening duration.

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1. INTRODUCTION

Acute diarrhea continues to pose a major public health issue worldwide, especially in developing countries.[1,2] It is estimated to cause nearly 1.7 billion episodes annually in children under five, contributing substantially to pediatric morbidity and mortality, primarily due to dehydration and electrolyte imbalance.[3] In Indonesia, diarrhea consistently ranks among the top causes of post-neonatal and under-five mortality, with South Sulawesi reporting high prevalence rates, necessitating optimized management strategies.[4]

The World Health Organization (WHO) advises a typical five-step approach for handling acute diarrhea, which highlights the use of oral rehydration solution (ORS), zinc supplements, maintaining feeding, targeted antibiotic application, and educating caregivers.[5] While this standard therapy effectively prevents and treats dehydration, it does not consistently shorten the duration of the illness or rapidly alleviate symptoms, leading to prolonged discomfort and increased healthcare utilization.[6,7] Consequently, there is growing interest in adjunctive therapies, particularly probiotics, to accelerate clinical recovery.[8,9]

Saccharomyces boulardii, a non-pathogenic, transient yeast probiotic, has demonstrated unique advantages over bacterial probiotics.[10,11] It is naturally resistant to antibiotics and gastric acidity, allowing it to survive transit to the colon.[12] Its mechanisms of action include the secretion of proteases that neutralize bacterial toxins, enhancement of intestinal barrier function, modulation of the local immune response, and stimulation of brush-border enzyme activity.[13,14] Despite existing literature, there is a lack of double-blind, randomized controlled trials (RCTs) in Indonesia specifically evaluating the clinical trajectory of *S. boulardii* as a single-strain adjunct in non-specific acute pediatric diarrhea.[15] The objective of this study is to assess how effective S. boulardii is in speeding up clinical recovery within a local hospital environment, offering evidence-based recommendations for pediatric practice.

2. MATERIALS AND METHODS

2.1 Study design and settings

From November 2025 to January 2026, a prospective, double-blind, randomized, placebo-controlled trial was conducted in the pediatric wards and emergency departments of three tertiary hospitals in Makassar, Indonesia. The study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized trials.

2.2 Study subjects

Sixty children, ranging in age from 6 months to 5 years, were diagnosed with acute non-specific diarrhea (≥3 loose/watery stools in 24 hours for <14 days) with no or mild dehydration. To be included, parents or legal guardians needed to provide written informed consent. Participants were excluded if they had severe malnutrition, chronic illnesses such as congenital heart disease or chronic kidney disease, were in immunocompromised states, or had used probiotics or antibiotics in the 7 days preceding enrollment. Drop-out criteria included progression to persistent diarrhea or mortality. Participant selection followed the recruitment flowchart (Figure 1).

2.3 Interventions and outcome measures

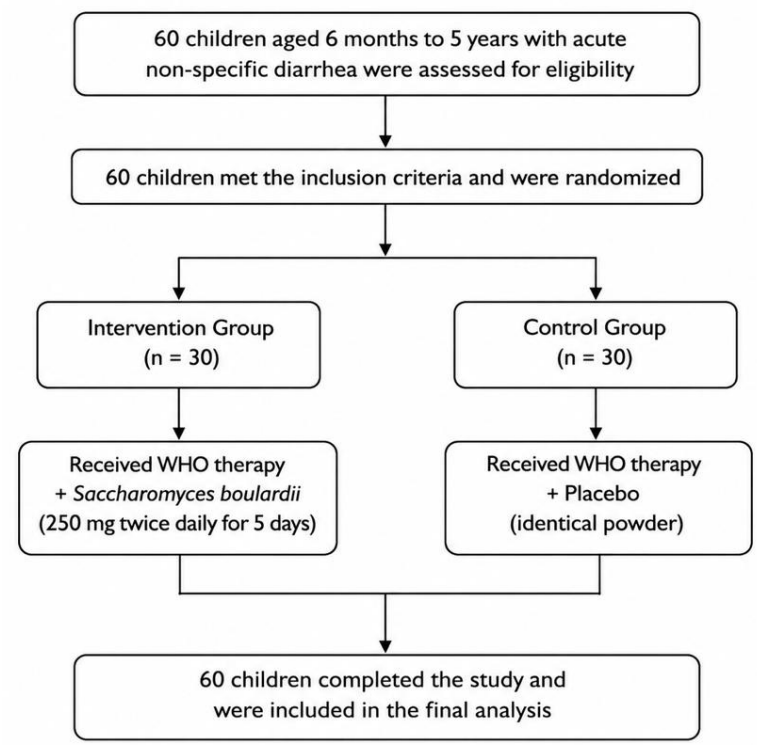
Participants who met the eligibility criteria were assigned randomly in a 1:1 ratio through a computer-generated random number table, ensuring allocation was concealed. The assignment remained unknown to both the investigators and the participants. The intervention group (n=30) received standard WHO therapy (ORS and zinc 20 mg/day for 10 days) plus S. boulardii (Normagut® powder, 250 mg [2.5 x 10^9 CFU] twice daily for 5 days). The control group (n=30) received standard WHO therapy plus an identical-appearing placebo powder for 5 days. Primary outcomes were daily diarrhea frequency (episodes per 24 hours) and stool consistency (categorized as watery, soft, or solid) assessed over 5 days. The secondary outcome was the total duration of diarrhea.

2.4 Statistical analysis

SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was employed for data analysis. The Shapiro-Wilk test was utilized to evaluate normality. To compare baseline characteristics, the Chi-square test or Fisher's Exact test was applied for categorical variables, while the Mann-Whitney U test was used for continuous variables that did not follow a normal distribution. The Wilcoxon signed-rank test and Marginal Homogeneity test were used to analyze changes in diarrhea frequency and stool

consistency within groups over time, respectively. Comparisons between groups were conducted using the Mann-Whitney U test. A p-value of less than 0.05 was deemed statistically significant.

Figure 1. Flowchart of participant enrollment



3. RESULTS AND DISCUSSION

3.1 Participant characteristics

Sixty children in total participated in the study, with 30 assigned to the intervention group and 30 to the control group. The initial demographic and clinical features were evenly matched across both groups. Table 1 shows that randomization was effective, as there were no statistically significant differences in the distribution of sex ($p = 0.796$), median age ($p = 0.106$), or nutritional status ($p = 0.112$).

3.2 Diarrhea frequency

Analysis within each group revealed that the frequency of diarrhea significantly decreased from Day 1 to Day 5 in both the intervention group ($p < 0.001$) and the control group ($p < 0.001$). Between-group comparison revealed that the intervention group experienced a significantly faster reduction in diarrhea frequency starting from Day 2 through Day 5 ($p < 0.05$ for all days) (Table 2).

Table 1. Baseline Characteristics of the Study Groups

Variable	Group A: Yeast Probiotics (n=30)	Group B: Placebo (n=30)	P value
Gender			
Boy	17 (56.7%)	15 (50%)	0.796*
Girl	13 (43.3%)	15 (50%)	

Age (Month) Median (Range)	18.5 (5-60)	24.0 (6-60)	0.106**
Nutritional status			
Normal	0	2 (6.7%)	0.112***
Underweight	30 (100%)	26 (86.7%)	
Obese	0	2 (6.7%)	

*Chi-square test; **Mann-Whitney U test; ***Fisher's exact test. Values are presented as n (%) or median (range), as appropriate.

Table 2. Frequency of diarrhea in Yeast Probiotics Group Compared to Placebo

Frequency of Diarrhea	Group A: Yeast Probiotics (n=30)	Group B: Placebo (n=30)	P value
Day 1	5.00 (3-12)	5.00 (3-11)	0.250 *
Day 2	4.00 (1-8)	5.00 (2-8)	0.000 *
Day 3	2.00 (1-6)	4.00 (2-6)	0.000 *
Day 4	1.00 (0-3)	2.00 (1-4)	0.035 *
Day 5	1.00 (0-2)	1.00 (1-2)	0.003 *

*Mann-Whitney U test. Values are presented as median (range). $p < 0.05$ was considered statistically significant.

3.3 Duration of diarrhea

In the intervention group, the median length of diarrhea was 3 days, with a range of 1 to 4 days, while in the control group, it was also 3 days, but ranged from 2 to 4 days. The difference between the two groups was not statistically significant ($p = 0.584$). (Table 3).

Table 3. Duration or Length of Stay in Children Between Yeast Probiotics and Placebo Groups

Duration of Diarrhea (Day)	Group A: Yeast Probiotics (n=30)	Group B: Placebo (n=30)	P Value
Median	3.00 (1-4)	3.00 (2-4)	0.584*

*Mann-Whitney U test. Values are presented as median (range). $p < 0.05$ was considered statistically significant.

3.4 Stool consistency

The intervention group demonstrated a significantly faster normalization of stool consistency. By Day 5, 96.7% of children in the intervention group had achieved solid stool, whereas 100% of children in the control group still had soft stool ($p < 0.001$) (Table 4). Analysis of the groups showed that the intervention group achieved a notably quicker normalization of stool consistency from Day 2 to Day 5, with statistical significance on each day ($p < 0.05$) (Table 5).

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Table 4. Stool Consistency in Each Group

Stool Consistency	Group A Yeast probiotics (n=30)		P value	Group B Placebo (n=30)		P value
	Day 1	Day 5		Day 1	Day 5	
Watery	30 (100%)	0	0.000*	30 (100%)	0	0.000*
Soft	0	1 (3.3%)		0	30 (100%)	
Solid	0	29 (96.7%)		0	0 (0%)	

*Marginal homogeneity test. Values are presented as n (%). $p < 0.05$ was considered statistically significant.

Table 5. Stool Consistency of Yeast Probiotics and Placebo Groups

Faeses Consistency	Group A: Yeast Probiotics (n=30)	Groups B: Placebo (n=30)	P value
Day 2			
Watery Soft	13 (43.3 %)	24 (80 %)	0.008*
Solid	17 (56.7 %)	6 (20.0 %)	
	0	0	
Day 3			
Watery Soft	2 (6.7%)	12 (40.0%)	0.000*
Solid	19 (63.3%)	18 (60.0%)	
	9 (30.0%)	0 (0.0%)	
Day 4			
Watery Soft	0 (0.0%)	0 (0.0%)	0.000*
Solid	8 (26.7%)	30 (100 %)	
	22 (73.3%)	0 (0.0%)	
Day 5			
Watery Soft	0(0.0)	0 (0.0%)	0.000*
Solid	1 (3.3 %)	30 (100 %)	
	29 (96%)	0 (0.0 %)	

*Chi-square test. Values are presented as n (%). $p < 0.05$ was considered statistically significant.

3.5 Discussion

This double-blind RCT demonstrates that the adjunctive use of *Saccharomyces boulardii* significantly accelerates clinical recovery in children with acute non-specific diarrhea, primarily evidenced by a faster reduction in stool frequency and more rapid normalization of stool consistency compared to standard therapy alone.

Our findings regarding diarrhea frequency align with previous RCTs. Sharif et al. and Mourey et al. similarly reported that *S. boulardii* significantly reduces the number of daily bowel movements in pediatric acute diarrhea compared to placebo.[16,17] The biological plausibility of this clinical improvement is supported by the actions of S. boulardii. It has direct antimicrobial properties and releases a 54-kDa protease that breaks down bacterial toxins, including those produced by *E. coli* and *C. difficile*. This process helps to decrease both intestinal secretory reactions and inflammation.[13,18]

Furthermore, our study highlights a highly significant improvement in stool consistency. By Day 5, nearly all children in the intervention group had formed, solid stools, whereas the control group predominantly had soft stools. This can be attributed

to the trophic effects of *S. boulardii*. Yeast enhances the function of brush-border enzymes such as lactase and sucrase, while also boosting the generation of short-chain fatty acids (SCFAs) like butyrate. This process aids in the absorption of water and electrolytes in the colon, thereby directly improving stool consistency.[14,19]

It is intriguing that although clinical improvement occurred more rapidly, the median duration of diarrhea remained the same at 3 days across both groups in our cohort, with no significant difference observed ($p = 0.584$). This contrasts with some meta-analyses that report a reduction in overall duration.[20] This discrepancy may be due to our relatively small sample size (n=60), or the fact that standard therapy (ORS + Zinc) is already highly effective at resolving mild-to-moderate diarrhea within a few days, creating a "floor effect." Nevertheless, the faster daily reduction in frequency and earlier achievement of solid stool are clinically meaningful, as they reduce caregiver anxiety, improve patient comfort, and may indirectly reduce the length of hospital stay.

The study's main advantage lies in its stringent design, characterized by a double-blind, randomized, placebo-controlled approach that effectively reduces both selection and performance biases. Additionally, by carrying out the trial in three different hospitals in Makassar, the applicability of the results to the local community is significantly improved. Limitations include the lack of stool PCR or culture to identify specific viral or bacterial pathogens, which prevents subgroup analysis of pathogen-specific efficacy. Additionally, diarrhea frequency relied partly on parental reporting, which may introduce minor recall bias.

4. CONCLUSION

Incorporating *Saccharomyces boulardii* as an adjunctive treatment notably hastens the decrease in diarrhea frequency and aids in normalizing stool consistency among children experiencing acute non-specific diarrhea. Although the total duration of diarrhea did not show a significant reduction in this group, the swift enhancement in daily clinical indicators justifies the use of *S. boulardii* as a safe and effective supplement to the standard WHO management protocols in pediatric care.

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AUTHOR CONTRIBUTIONS

Study conception and design: AM, SL; data collection: AM; analysis and interpretation of results: AM, SL, RA; draft manuscript preparation: AM, SL, RA, AL, MA, SP, AA. All authors reviewed the results and approved the final version of the article.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

ETHICS STATEMENT

The study was approved by the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University (date: [approval date]; number: 889/UN4.6.4.5.3.1/PP36/2025). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participants before enrollment.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request, subject to applicable ethical and institutional restrictions.

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