

The Effect of Administering the Probiotic *Lactiplantibacillus Plantarum* DAD-13 on Procalcitonin Levels, C-Reactive Protein, and Interleukin-6 in Sepsis Patients in the Intensive Care Unit of H. Adam Malik Hospital, Medan

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Abstract

Sepsis remains a major global health issue with high morbidity and mortality rates, particularly in intensive care units (ICU). This study investigated the effects of administering the probiotic *Lactiplantibacillus plantarum* Dad-13 on inflammatory markers (procalcitonin [PCT], C-reactive protein [CRP], interleukin-6 [IL-6]) and defecation profiles in sepsis patients admitted to the ICU at RSUP H. Adam Malik Medan. A randomized, double-blind, placebo-controlled clinical trial was conducted with 30 sepsis patients divided into two groups: one receiving *L. plantarum* Dad-13 (2 capsules/day for 4 days) and the other a placebo. Biomarker levels and defecation frequency/consistency were monitored. Trial registration: ClinicalTrials.gov Identifier: NCT07072871, registered on 21 July 2025. Retrospectively registered.

Results showed a clinical reduction in PCT, CRP, and IL-6 levels in the probiotic group compared to the placebo group, though the changes were not statistically significant ($p > 0.05$). Defecation frequency and stool consistency improved significantly in the probiotic group by days 3 and 4 ($p < 0.05$), indicating enhanced gut microbiota balance. The study suggests that *L. plantarum* Dad-13 may aid in modulating inflammatory responses and improving gastrointestinal function in sepsis patients, albeit further research with longer intervention periods and larger samples is needed to confirm these findings.

Introduction

Sepsis continues to pose a major challenge in modern medicine as a leading cause of multiorgan failure with high morbidity and mortality, especially among critically ill patients. Globally, over 30 million sepsis cases occur annually, with around 5.3 million deaths (Li et al., 2016). In Asia, sepsis prevalence in intensive care units (ICUs) is about 22.4%, with variations depending on a country's income level. One of the key mechanisms that exacerbates sepsis is dysregulation of the host immune response, which contributes to organ dysfunction and disease progression. This immune disruption significantly impacts not only vital organs such as the lungs, kidneys, and heart but also the gastrointestinal system, which often remains clinically unnoticed due to its nonspecific symptoms (Fay et al., 2019).

Sepsis also induces significant changes in the gut environment and microbiota composition. Within hours of ICU admission, a substantial decline in gut microbial diversity occurs, indicating severe dysbiosis. This dysbiosis compromises intestinal mucosal integrity, increases proinflammatory cytokine production, and facilitates the translocation of toxins that trigger systemic organ injury through the gut-organ axis (Fay et al., 2019). Moreover, conventional treatments such as broad-spectrum antibiotics may worsen dysbiosis by disrupting commensal flora and promoting antimicrobial resistance.

In this context, probiotic therapy offers a promising alternative as both an immunomodulator and a restorative agent for microbial homeostasis. Probiotics have been shown to inhibit pathogenic colonization, support gut flora, and modulate immune responses through complex mechanisms involving interactions with immune cells (macrophages, T-cells, B-cells) and regulation of cytokine expression (Wischmeyer et al., 2016). Studies have reported benefits of probiotics in reducing sepsis-

related complications, including findings from Gong et al. (2019) and meta-analyses demonstrating a reduction in late-onset sepsis incidence.

The probiotic strain used is crucial to therapeutic effectiveness. One promising candidate is *Lactiplantibacillus plantarum*, particularly the Indonesian strain DAD-13, isolated from fermented buffalo milk. This strain is known for its resilience in the digestive tract and demonstrated antibacterial, anti-inflammatory, and immune-boosting properties (Darmastuti et al., 2021; Nurliyani et al., 2022). Additionally, *L. plantarum* can inhibit MAPK and NF- κ B signaling pathways and reduce TLR4 expression, which are directly related to lowering levels of PCT, CRP, and IL-6 (Tsilika et al., 2021; Miri et al., 2022).

Despite its potential, the use of *L. plantarum* DAD-13 in adult ICU sepsis patients has not been previously studied. Since probiotic products like Vipilac®—which contain this strain—are approved and widely used in Indonesia, it is important to assess the effect of *L. plantarum* DAD-13 on inflammatory biomarkers such as IL-6, CRP, and PCT in this clinical setting.

Material and Methods

This study was a randomized, double-blind, placebo-controlled clinical trial conducted to evaluate the effects of administering *Lactiplantibacillus plantarum* DAD-13 on inflammatory markers (PCT, CRP, IL-6) in sepsis patients admitted to the ICU of H. Adam Malik General Hospital, Medan. Ethical clearance was obtained from the Health Research Ethics Committee of Universitas Sumatera Utara, and hospital approval was granted.

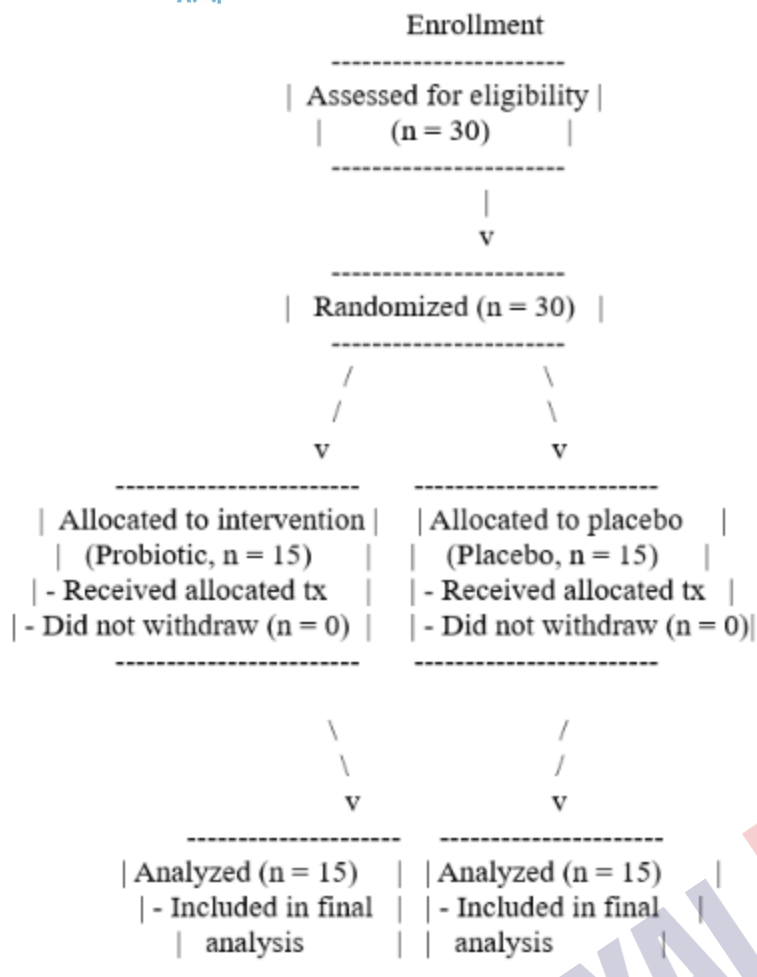
Participants included adult ICU patients (aged 18–65) newly diagnosed with sepsis, using nasogastric tubes (NGT), and receiving enteral feeding of 1500–2000 kcal/day. Exclusion criteria included gastrointestinal disorders, immunocompromised conditions, vascular devices, or probiotic allergies.

Participants were randomized into two groups via randomizer.org: the intervention group received *L. plantarum* DAD-13 capsules (Vipilac®), and the control group received placebo (maltodextrin capsules). The intervention lasted four days, with all patients continuing to receive standard sepsis management as per the Surviving Sepsis Campaign 2021.

Blood samples were collected on day 1 (T0) and day 4 (T1) to measure IL-6, CRP, and PCT levels using ELISA. All measurements were conducted in a blinded fashion to ensure objectivity. This trial was designed and reported in accordance with the CONSORT 2010 guidelines for randomized controlled trials (<http://www.consort-statement.org>).

Results

This study was conducted and reported in accordance with the CONSORT 2010 guidelines for randomized clinical trials.



Thirty ICU sepsis patients were enrolled and randomized equally into the probiotic group (n=15) and placebo group (n=15). Both groups were comparable in demographic and clinical characteristics at baseline, enabling a valid assessment of the intervention's effects.

Karakteristik	Kelompok Probiotik (n = 15)	Kontrol (n = 15)	p value	Total (n = 30)
Age (year)				
Mean±SD	48,67±12,1	45,46±11,28	0,461 [#]	47,06±11,64
Gender (n[%])				
Male	11 (73,3%)	6 (40%)	0,065*	17 (56,7%)
Female	4 (26,7%)	9 (60%)		13 (43,3%)
Weight (kg)	61,18±8,69	55,98±8,79	0,115 [#]	58,58±8,99
Height (cm)	166±7,57	161,93±7,75	0,157 [#]	163,96±7,8
BMI (kg/m ²)	22,05±1,35	21,18±1,45	0,101 [#]	21,62±1,45
Albumin (gr/dL)	3,04±0,22	3,0±0,42	0,77 [#]	3,02±0,33
SOFA Score	5,4±1,88	5,33±1,54	0,272 [#]	5,37±1,69
Diagnosis (n[%])				
Respiratory	10 (66,7%)	7 (46,7%)	0,749*	17 (56,7%)
Urogenital	2 (13,3%)	3 (20%)		5 (16,7%)
SSTI	2 (13,3%)	3 (20%)		5 (16,7%)
Musculoskeletal	1 (6,7%)	1 (6,7%)		2 (6,7%)
Nervous system	0 (0%)	1 (6,7%)		1 (3,3%)
Mechanical Ventilation	15 (100%)	15 (100%)	1,00*	30 (100%)

*Uji *Chi Square*; [#]Uji T Independen

In the probiotic group, median PCT levels declined from 3.39 ng/mL to 1.13 ng/mL, CRP from 0.7 mg/L to 0.5 mg/L, and IL-6 from 79.47 pg/mL to 77.92 pg/mL. Though not statistically significant, the decrease in PCT approached significance (p = 0.061), suggesting a potential biological effect.

Variabel	Periode Pemeriksaan (Median[Min-Max])		p value*
	T0	T1	
IL-6	79,47 (8,66 – 333,23)	77,92 (17,97 – 288,8)	0,91
PCT	3,39 (0,22 – 160,4)	1,13 (0,16 – 128,4)	0,061
CRP	0,7 (0,5 – 14,2)	0,5 (0,5 – 10,8)	0,261

*Uji Wilcoxon

In contrast, the placebo group showed clinical increases in IL-6 (from 97.53 to 146.9 pg/mL), PCT (1.32 to 2.5 ng/mL), and CRP (0.7 to 1.4 mg/L), none of which reached statistical significance. Between-group comparisons on day 4 revealed lower biomarker levels in the probiotic group, with p-values of 0.084 (IL-6), 0.174 (PCT), and 0.250 (CRP), indicating a non-significant but favorable trend.

Variabel	Periode (Median [Min-Max])		p value*
	T0	T1	
IL-6	97,53 (22,06 – 300,36)	146,9 (34,47 – 338,31)	0,156
PCT	1,32 (0,09 – 108,5)	2,5 (0,72 - 106)	0,155
CRP	0,7 (0,5 – 3,02)	1,4 (0,5 – 39,2)	0,062

*Uji Wilcoxon

Significant improvements were observed in the probiotic group's gastrointestinal outcomes. By days 3 and 4, defecation frequency and stool consistency had normalized in most probiotic patients, showing a statistically significant difference compared to controls ($p < 0.05$).

Variabel	Probiotic Group		Control Group		p value*	RR (95% CI)
	n	%	n	%		
H1	7	46,7	7	46,7	1,00	1,00 (0,51 – 1,95)
H2	8	53,3	5	33,3	0,27	0,7 (0,37 – 1,34)
H3	13	86,7	5	33,3	0,03	0,2 (0,05 – 0,76)
H4	14	93,3	7	46,7	0,04	0,12 (0,02 – 0,88)
*Uji Chi Square						

Time	Intervention	Defecacy Consistension (n[%])			Total	p value*
		Hard	Normal	Soft		
H1	Probiotik	3 (42,86%)	3 (42,86%)	1 (14,28%)	7	0,751
	Kontrol	2 (28,57%)	2 (28,57%)	3 (42,86%)	7	
H2	Probiotik	1 (12,5%)	6 (75%)	1 (12,5%)	8	0,223
	Kontrol	0	4 (80%)	1 (20%)	5	
H3	Probiotik	0	13 (100)	0	13	0,001
	Kontrol	1 (20%)	1 (20%)	3 (60%)	5	
H4	Probiotik	0	14 (100%)	0	14	0,014
	Kontrol	2 (28,57%)	3 (42,86%)	2 (28,57%)	7	
*Uji <i>Mann-Whitney</i>						

This suggests beneficial modulation of gut microbiota, often impaired in sepsis patients due to critical illness and antibiotic use.

Discussion

This study aimed to evaluate the effect of administering the probiotic *Lactiplantibacillus plantarum* DAD-13 on inflammatory biomarkers—namely IL-6, CRP, and PCT—in sepsis patients admitted to the intensive care unit. Although no statistically significant differences were found, the results demonstrated a downward trend in inflammatory biomarkers in the probiotic group compared to the placebo group. The most notable decrease occurred in PCT levels, with a p-value of 0.061, indicating potential clinical significance despite not reaching conventional statistical thresholds.

PCT is a specific biomarker for systemic infection and is widely used for diagnosing and evaluating therapeutic response in sepsis. The sharper decline in PCT levels in the probiotic group suggests a potential improvement in systemic inflammatory response due to the immunomodulatory effects of the probiotic. This aligns with findings from Miri et al. (2022), which showed that *L. plantarum* administration suppressed proinflammatory cytokines, including IL-6 and TNF- α , by inhibiting the TLR4/NF- κ B pathway. The concurrent reductions in IL-6 and CRP levels observed in this study further support the hypothesis that probiotics act through modulation of the innate immune system.

This effect may be reinforced by the fact that *L. plantarum* DAD-13 is a locally derived strain that has demonstrated strong resilience in the gastrointestinal tract, along with antibacterial and anti-inflammatory properties. Several preclinical studies have shown that this strain enhances IgA production, reduces pathogenic colonization (such as *Escherichia coli*), and improves the condition of intestinal mucosa (Darmastuti et al., 2021; Nurliyani et al., 2022). These findings suggest that *L.*

plantarum DAD-13 not only modulates systemic immune responses but also restores gastrointestinal integrity disrupted by sepsis and intensive antibiotic therapy.

Intestinal microbiota imbalance (dysbiosis) is a key factor in the pathogenesis of sepsis through the gut-organ axis. In sepsis, increased mucosal permeability facilitates endotoxin and microbial translocation into systemic circulation, exacerbating inflammation and leading to multiorgan dysfunction. Probiotics help restore intestinal eubiosis and prevent further barrier damage, thereby reducing systemic inflammatory stimuli (Fay et al., 2019).

This study also noted improvements in defecation frequency and quality in the probiotic group, which can serve as indirect indicators of gastrointestinal function recovery. This is significant because gut function is often overlooked in sepsis management, despite its central role in numerous immunological and metabolic pathways. The probiotic's role in improving gut function reinforces its potential as a complementary therapy in an integrative approach to sepsis.

Nonetheless, several limitations must be considered. The short intervention duration (4 days), small sample size, and concurrent treatments such as broad-spectrum antibiotics and opioids—which may affect gut microbiota—are factors that could influence the observed effects and limit the detection of statistically significant differences. Further research with larger sample sizes, extended intervention periods, and better control of confounding variables is needed to validate these findings and explore the underlying molecular mechanisms.

Considering all these findings, *L. plantarum* DAD-13 may be considered a supportive intervention in sepsis management, particularly in helping regulate systemic inflammation and maintain gastrointestinal function in ICU patients. This study provides an important early contribution to the development of locally sourced, microbiome-based therapies that are safe and potentially beneficial for critically ill patients.

Conclusion

Administering *Lactiplantibacillus plantarum* DAD-13 to ICU sepsis patients resulted in decreased levels of IL-6, PCT, and CRP, with notable clinical improvement in gastrointestinal function. While statistical significance was not achieved, the trends suggest that *L. plantarum* DAD-13 has potential as an adjunct immunomodulatory therapy for sepsis.

These findings support the safety and tolerability of probiotic interventions in critical care and highlight the need for further studies exploring local probiotic strains in severe illness contexts.

Abbreviations

ICU : Intensive Care Unit

PCT : Procalcitonin

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Inform consent was obtained from all the participants.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Data supporting the conclusions of this study are included in the article and its additional files.

COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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AUTHOR'S CONTRIBUTIONS

Z wrote the main manuscript

AH wrote the main manuscript

APL wrote the main manuscript

YY wrote the main manuscript

All authors reviewed the manuscript

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REPORTING GUIDELINES

References

1. Dang, A. T., & Marsland, B. J. (2019). Microbes, metabolites, and the gut–lung axis. *Mucosal Immunology*, 12(4), 843–850.
2. Darmastuti, N., et al. (2021). Efektivitas *Lactiplantibacillus plantarum* DAD-13 dalam menurunkan jumlah koloni *Escherichia coli* di kolon pada tikus. *Laporan Penelitian*, Universitas Gadjah Mada.
3. Fay, K. T., Ford, M. L., Coopersmith, C. M. (2019). The intestinal microenvironment in sepsis. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1865(5), 1129–1135.
4. Gong, J., et al. (2019). Effects of probiotics on liver injury induced by sepsis in murine models. *Journal of Hepatology Research*, 4(2), 34–42.
5. Kim, S. K., et al. (2017). Immunomodulatory effects of *Lactobacillus plantarum* lysates on lipopolysaccharide-stimulated macrophages via MAPK and NF-κB signaling pathways. *Nutrition Research and Practice*, 11(2), 97–104.
6. Li, Y., et al. (2016). The epidemiology of sepsis in intensive care units in Asia. *Critical Care Medicine*, 44(8), e377–e386.
7. Miri, H., et al. (2022). *Lactobacillus plantarum* from fermented soy suppresses inflammation in septic rats. *Nutrition Research*, 102, 35–45.
8. Nurliyani, N., et al. (2022). Kombinasi probiotik *L. plantarum* DAD-13 dan serat ubi jalar meningkatkan kadar IgA di saluran cerna tikus. *Jurnal Ilmu Ternak*, 22(1), 34–42.
9. Tsilika, M., et al. (2021). Early administration of probiotics in ICU patients reduces incidence of ventilator-associated pneumonia and sepsis. *Clinical Nutrition*, 40(2), 507–515.
10. Wischmeyer, P. E., et al. (2016). Role of the microbiome, probiotics, and ‘dysbiosis therapy’ in critical illness. *Current Opinion in Critical Care*, 22(4), 347–353.