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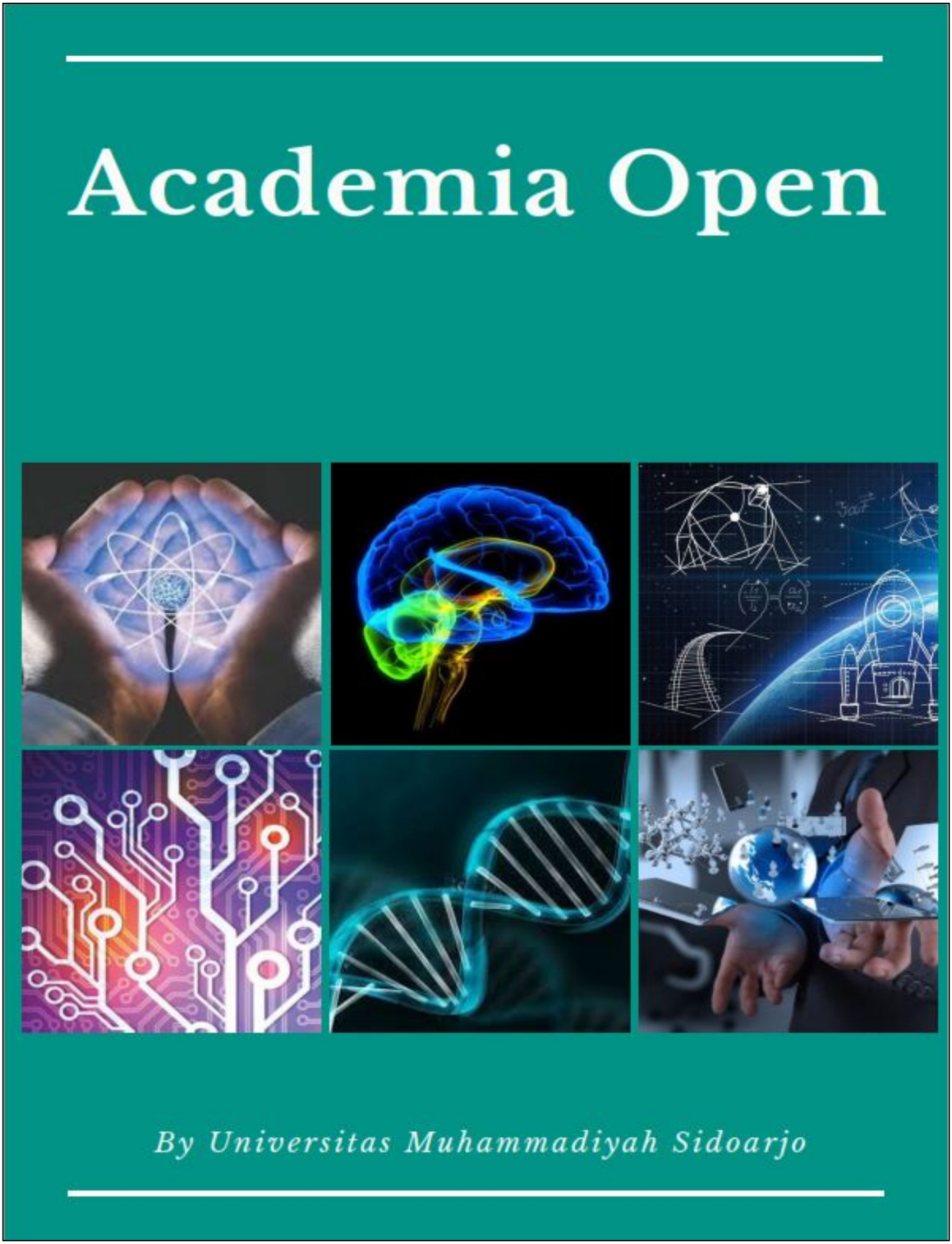

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Escherichia coli Triggers Intestinal Inflammation and Mucosal Damage Through Immune Activation

Escherichia coli Memicu Peradangan Usus dan Kerusakan Mukosa Melalui Aktivasi Kekebalan Tubuh

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Abstract

General Background: The intestinal mucosa plays a crucial role in immune defense and homeostasis. **Specific Background:** Pathogenic *Escherichia coli* (*E. coli*) infection disrupts this balance, triggering immune responses and inflammation. **Knowledge Gap:** The detailed immune mechanisms underlying *E. coli* infection, including cytokine production and immune cell infiltration, remain poorly understood. **Aims:** This study investigates the immune responses, cytokine production, and mucosal damage induced by *E. coli* infection. **Results:** Using murine models and clinical samples, *E. coli* infection resulted in elevated cytokine levels (TNF-α, IL-6, IL-1β), increased immune cell infiltration (neutrophils, macrophages, T cells), and mucosal damage, such as reduced villus height and increased crypt depth. **Novelty:** This research provides comprehensive insights into the immunological and histopathological consequences of *E. coli* infection, integrating cytokine analysis, immune profiling, and tissue damage assessment. **Implications:** The findings highlight potential therapeutic targets for preserving intestinal mucosal integrity and reducing systemic inflammation. Future studies should focus on exploring molecular mechanisms and developing interventions to mitigate the impact of *E. coli* infections.

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Highlights:

1. *E. coli* disrupts intestinal mucosa, triggering immune responses and inflammation.
2. Investigate immune responses, cytokine production, and mucosal damage due to *E. coli*.
3. Elevated cytokines, immune cell infiltration, and mucosal damage highlight systemic inflammation.

Keywords: *E. coli*, immunity, intestine

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Introduction

The gastrointestinal tract is a complex and dynamic system essential for nutrient absorption, microbiota-host interactions, and immune defense (1). The intestinal mucosa acts as a critical barrier against pathogens while maintaining tolerance to commensal microorganisms (2). However, infections by pathogenic organisms, such as *Escherichia coli* (*E. coli*), can disrupt this delicate balance, triggering immune responses that contribute to disease pathology (3).

E. coli is not a singular entity but rather a diverse group of strains, ranging from harmless commensals to highly virulent pathogens, including enterohemorrhagic (EHEC), enteropathogenic (EPEC), and enterotoxigenic (ETEC) E. coli (4,5). This diversity adds a layer of complexity to our research as we seek to understand the immune responses triggered by these various strains (6).

The immune response to *E. coli* infection involves complex interactions between epithelial cells, immune cells, and the gut microbiota. Critical components of this response include (7,8):

1. Cytokine Production: Pathogens stimulate the release of cytokines such as TNF-α, IL-6, and IL-1β, which mediate inflammation and recruit immune cells to the site of infection.

2. Immune Cell Recruitment: Neutrophils, macrophages, and T cells regulate pathogen clearance and inflammation.

3. Mucosal Damage: Disruption of epithelial integrity leads to increased intestinal permeability, bacterial translocation, and systemic inflammation.

Despite extensive research, gaps remain in understanding how these mechanisms contribute to disease progression and severity. This study explores the impact of *E. coli* infection on the immune responses of the intestinal mucosa, focusing on cytokine dynamics, immune cell activity, and histopathological changes.

Methods

Study Design:

This study included 30 mice were divided into two groups in equal number:

1. Control Group: Healthy murine models and clinical samples from individuals without *E. coli* infection.

2. Infected Group: Murine models and clinical samples from patients with confirmed pathogenic *E. coli* infections.

Key Methods:

a. Cytokine Analysis: Cytokines (TNF-α, IL-6, IL-1β, IL-10) were quantified using enzyme-linked immunosorbent assays (ELISA) from Mybiosource company.

b. Immune Cell Quantification: Flow cytometry measured immune cell populations, including neutrophils, macrophages, and T cells.

c. Histological Analysis: Intestinal tissue samples were stained with hematoxylin and eosin (H&E) to evaluate mucosal damage, including villus height and crypt depth.

d. C-reactive protein: using the spectrophotometer method and kit from Biolabo company.

StatisticalAnalysis: Results were analyzed using ANOVA for group comparisons and Pearson's correlation for relationships between variables, with $p < 0.05$ considered statistically significant.

Result And Discussion

Result

Cytokine	Control (pg/mL)	Infected (pg/mL)	p-value
TNF-α	10 ± 2	50 ± 5	< 0.001
IL-6	15 ± 3	70 ± 6	< 0.001
IL-1β	8 ± 1	45 ± 4	< 0.001

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IL-10	12 ± 2	25 ± 3	< 0.01

Table 1. ***Cytokine Levels in Intestinal Tissue Post-*** ***E.*** ***coli*** ***Infection***

Elevated levels of pro-inflammatory cytokines were observed, indicating a robust immune activation in response to *E. coli* infection.

Immune Cell Type	Control (% of total cells)	Infected (% of total cells)	p-value
Neutrophils	5 ± 1	30 ± 3	< 0.001
Macrophages	10 ± 2	25 ± 3	< 0.001
T cells (CD4+)	20 ± 3	35 ± 4	< 0.01
T cells (CD8+)	15 ± 2	40 ± 4	< 0.01

Table 2. ***Immune Cell Infiltration in Intestinal Mucosa***

Significant increases in immune cell infiltration suggest robust innate and adaptive immune activation.

Parameter	Control	Infected	p-value
Villus height (µm)	400 ± 20	200 ± 15	< 0.001
Crypt depth (µm)	150 ± 10	300 ± 20	< 0.001
Goblet cell density	50 ± 5	25 ± 4	< 0.01

Table 3. ***Histopathological Changes in Intestinal Tissue***

Mucosal damage, including reduced villus height and increased crypt depth, was evident, impairing intestinal function.

Marker	Control (ng/mL)	Infected (ng/mL)	p-value
C-reactive protein (CRP)	2 ± 0.5	10 ± 1.5	< 0.001

Table 4. ***Systemic Inflammatory Markers in Serum***

Elevated systemic markers of inflammation reflect the spillover of local intestinal inflammation into systemic circulation.

Discussion

The findings of this study provide critical insights into the impact of Escherichia coli (E. coli) infection on immune responses in the intestinal mucosa. The data reveal significant alterations in cytokine levels, immune cell infiltration, and mucosal structure, underscoring the multifaceted nature of the host-pathogen interaction during E. coli infection.

The elevated cytokine levels observed in the infected group demonstrate the activation of the immune system in response to E. coli. Pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, are known mediators of the inflammatory response (9). These cytokines are produced by epithelial cells, macrophages, and neutrophils upon recognition of pathogen-associated molecular patterns (PAMPs) like lipopolysaccharides (LPS) through toll-like receptors (TLRs) (10). The sharp increase in these cytokines highlights the innate immune system's attempt to contain and eliminate the infection (11). However, excessive cytokine production can exacerbate inflammation, leading to collateral tissue damage, epithelial barrier disruption, and systemic inflammation (12). The modest increase in IL-10, an anti-inflammatory cytokine, suggests a compensatory mechanism to counterbalance the inflammation (13). However, the insufficient levels of IL-10 relative to the pro-inflammatory cytokines indicate an imbalance that favors a pro-inflammatory environment (14).

Immune cell infiltration, particularly by neutrophils and macrophages, is a hallmark of acute inflammation. As the first responders, neutrophils play a crucial role in phagocytosis and releasing antimicrobial agents, such as reactive oxygen species and proteases (15). While effective in controlling bacterial replication, these mechanisms can inadvertently damage surrounding tissues. Similarly, macrophages, recruited to sustain the inflammatory response and clear apoptotic cells, may exacerbate tissue injury if their activity is dysregulated (16). The increased presence of T cells, particularly CD4+ helper T cells and CD8+ cytotoxic T cells, indicates the activation of the adaptive immune system. This response is critical for pathogen-specific immunity and the development of immune memory (17). However, the excessive infiltration of these cells can prolong inflammation and contribute to chronic intestinal damage if the infection is not resolved promptly.

Histopathological analyses revealed significant structural changes in the intestinal mucosa, including reduced villus

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height, increased crypt depth, and decreased goblet cell density. These alterations suggest severe epithelial damage caused by E. coli infection (18). The reduction in villus height compromises nutrient absorption, while increased crypt depth reflects hyperplasia, likely a compensatory mechanism to replenish lost epithelial cells. Goblet cells, which produce mucus to protect the epithelium, were significantly reduced in number, leading to impaired mucosal barrier function. This weakening of the barrier allows bacterial translocation and the leakage of microbial products into the bloodstream, fueling systemic inflammation and increasing the risk of complications such as sepsis (19).

Systemic inflammation, as evidenced by elevated levels of C-reactive protein (CRP) in the serum, highlights the potential of local intestinal inflammation to spill over into systemic circulation. CRP, an acute-phase reactant produced by the liver, is a marker of systemic inflammation and is closely associated with bacterial infections (20).

These findings have important implications for the development of therapeutic strategies. Modifying cytokine production could be a promising approach to mitigating excessive inflammation. Anti-inflammatory agents targeting TNF-α, IL-6, or IL-1β pathways may help restore the cytokine balance and reduce tissue damage (16). Additionally, therapies that enhance epithelial barrier integrity, such as probiotics, prebiotics, or agents promoting tight junction formation, could prevent bacterial translocation and systemic inflammation. Immunomodulatory agents that fine-tune the activity of neutrophils, macrophages, and T cells could further optimize the immune response, ensuring adequate pathogen clearance while minimizing collateral damage (14).

The study's findings also highlight the potential of histological parameters, cytokine profiles, and systemic inflammatory markers as diagnostic tools for assessing the severity of E. coli infections. Early detection and monitoring of these parameters could guide therapeutic interventions, improving patient outcomes (21).

Conclusion

E. coli infection significantly disrupts the intestinal mucosal immune response, leading to heightened inflammation, structural damage, and systemic consequences. These insights emphasize the importance of a balanced immune response and the need for targeted therapies that preserve mucosal integrity while effectively combating the infection. Future research should focus on unraveling the molecular mechanisms underlying these responses and exploring novel therapeutic approaches to mitigate the impact of E. coli infections.

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