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The Role of Probiotics As an Adjuvant Therapy for Sepsis Against Multidrug-Resistant Bacteria

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ABSTRACT

The impact of probiotics on sepsis, particularly when induced by multidrug-resistant (MDR) bacteria, is mediated through complex biochemical pathways. Probiotics demonstrate a capacity to effectively combat infections and reduce mortality rates in sepsis cases. A significant contributor to this efficacy is attributed to the short-chain fatty acids (SCFAs) produced by these probiotics. SCFAs play a critical role in modulating the immune system, primarily by influencing the production of inflammatory cytokines, fortifying the integrity of intestinal epithelium, preventing cellular apoptosis, and maintaining the balance of gut microbiota. Moreover, probiotics are instrumental in counteracting the detrimental impacts of excessive antibiotic use, which is a major contributing factor to the emergence of MDR bacterial strains. The integration of probiotics with conventional therapeutic approaches offers a viable and potentially effective strategy in the management of sepsis caused by MDR bacteria, suggesting a promising direction for future clinical interventions.

1. Introduction

Sepsis is a life-threatening medical condition caused by an excessive or uncontrolled immune response to bacterial infection, which can lead to organ dysfunction and death. The increasing prevalence of MDR bacteria exacerbates this challenge, with limited antibiotic choices and an increased risk of poor clinical outcomes.[1] Probiotics, as immunomodulators, offer an innovative approach through mechanisms that have the potential to restore microbiota balance and strengthen immune response.[2,3]

Recent research in the past few years has shown that probiotics have the potential to reduce mortality and improve clinical outcomes in sepsis patients, including cases involving multidrug-resistant bacteria. Probiotic administration is known to reduce death through immunomodulation mechanisms and increase immunoglobulin A (IgA) concentration, which plays an important role in maintaining homeostasis and mucosal barrier function against pathogens.[3,4] Probiotics also serve as immunonutrition to support the immune response of critically ill sepsis patients, although the mechanisms still need further study.[2] In addition, the use of probiotics has been associated with increased hemoglobin concentrations under systemic inflammation, indicating another role of probiotics in modulating the inflammatory response.[5]

In the context of antibiotic use, inappropriate administration has increased mortality and the growth rate of resistant bacteria.[6] It shows the potential of probiotics as an adjunct to conventional antibiotic therapy, paving the way for a more effective and comprehensive management strategy for sepsis.

2. Metabolites Produced by Probiotics

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. This definition was issued by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) emphasizing the importance of probiotics for human body health.[7]

Probiotics also have a role in the nutrient absorption process in the gut. Their metabolites can transform complex nutrients into simpler compounds that are easy for the body to absorb. One of the

beneficial metabolic products of fermentation is short-chain fatty acids (SCFAs) such as butyric acid, propionic acid, and acetic acid. SCFAs are short-chain organic acids produced from the fermentation of Non-digestible Carbohydrates (NDCs) by gut bacteria. In addition to SCFAs, gut bacteria can produce other organic acids, such as lactic acid. The organic acids formed can vary depending on the type of microorganism species and the available fiber and NDC supply in the gut.[8]

3. Probiotics Mechanisms of Action

Probiotics, often referred to as "good" or beneficial microorganisms, play an important role in maintaining human health. The mechanisms of action of probiotics in the human body are multifactorial and complex, involving interactions between probiotics, gut microbiota, and the host immune system.

Modulation of the Immune System. Probiotics interact with Toll-like receptors (TLRs) of immune cells in the gut, such as dendritic cells, lymphocytes, and macrophages. This interaction activates an immune response that helps fight infection and reduce inflammation.[9–11] Acetate, propionate, and butyrate SCFAs have been proven to have modulatory effects on the host immune system, including regulating the activity of immune cells and stimulating the production of anti-inflammatory cytokines. In addition, SCFAs can also influence the differentiation and function of immune cells, as well as affect the Th1/Th2 balance and Treg cell activity. This indicates that SCFAs produced by probiotics can play an important role as immunomodulators in maintaining the balance of the host immune system.[9]

Maintenance of Intestinal Epithelial Barrier Function. Probiotics strengthen intestinal epithelial integrity by reinforcing tight junctions between epithelial cells. This prevents the translocation of pathogenic bacteria and toxins into the bloodstream.[12] Probiotics can also enhance gut immune function by stimulating B cells to produce IgA through increased IL-6 production in a TLR2-dependent manner. In addition, probiotics can also trigger the release of serotonin in the gut by enterochromaffin (EC) cells that play a role in controlling gut motility and nerve signal transmission in the digestive tract. Gut serotonin can also affect mood balance, so it is often referred to as the "happiness hormone".[13]

Production of Antimicrobial Compounds. Probiotics produce antimicrobial compounds that can inhibit the growth of pathogenic bacteria in the gut.[9] Probiotics produce various antimicrobial substances, including bacteriocins, organic acids, and hydrogen peroxide. These play an important role in protecting the body from pathogenic hazards and maintaining gut microbiota balance.[11]

Nutrient Competition and Adhesion. Probiotics compete with pathogens for nutrients and adhesion sites on the gut wall, preventing colonization and growth of harmful bacteria. Probiotics also have co-aggregation ability where bacterial cells can adhere to cells of different bacterial species, thus protecting the host from pathogens by binding them.[10]

Influence on Host Metabolism. Probiotics influence host metabolism by interacting with gut microbiota, affecting nutrient absorption, and potentially modulating lipid and glucose metabolism.[9] Probiotics produce specific metabolites, so the effects are different. In the gut, probiotics can influence metabolism through the supply of additional enzymes and changes in the composition of the resident gut microbiota.[14]

4. Probiotics as an Adjunctive Therapy Approach for Sepsis

Sepsis is a life-threatening condition that requires intensive and effective management. The inflammation triggered by the infectious process can cause tissue damage and even multiple organ failure. The use of antibiotics as therapy sometimes exacerbates the condition due to gut dysbiosis. This change causes pathogenic bacteria to dominate and trigger damage to the digestive tract, increasing the risk of death.[15]

Sepsis can trigger apoptosis of gut epithelial cells due to excess pro-inflammatory cytokines and inflammatory mediators released, causing tissue damage and multiple organ failure. Cytokines such as TNF-α and IL-1β are known to induce apoptosis in various cells, including enterocytes. In addition, sepsis also disrupts microvascular blood flow to the gut, which can cause hypoxia and oxidative stress, both of which are apoptosis triggers. Hypoxia can activate transcription factors such as hypoxia-inducible factor (HIF)-1α, which plays a role in regulating the expression of genes related to apoptosis.[15,16]

Damage to the gut epithelium due to enterocyte apoptosis can cause bacterial and endotoxin translocation from the gut lumen into the systemic circulation, further exacerbating the inflammatory response and causing more damage to the epithelial barrier. [11,17] Probiotic supplementation by Angurana et al. reported beneficial decreases in proinflammatory cytokine levels such as interleukin-6 (IL-6), interleukin-12p70 (IL-12p70), interleukin-17 (IL-17), and tumor necrosis factor-alpha (TNF-α), as well as increased levels of anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta 1 (TGF-β1) on day 7 of administration in critically ill children with severe sepsis.[16]

Short Chain Fatty Acids (SCFAs) produced by probiotics can reduce inflammatory effects and enhance the survival rate of sepsis patients through inhibition of the NF-κB activation pathway in macrophages. This process occurs by reducing the activation of IκB kinase (IKK), necessary for the phosphorylation and degradation of the NF-κB

inhibitor (IκB). When IκB is not degraded, NF-κB remains bound and cannot translocate to the nucleus to activate target inflammatory genes, thus preventing the release of pro-inflammatory cytokines and reducing inflammation.[13,18,19]

Yilmaz, et al., in their study on the protective effects of Lactobacillus rhamnosus gg in sepsis-induced rats, also observed a decrease in C-reactive protein (CRP) and oxidative stress markers following probiotic administration.[20] CRP is a protein produced by the liver in response to acute inflammation, so its reduction may reflect an overall decrease in inflammatory activity, possibly involving modulation of inflammatory cytokines.[20,21]

Probiotics can also help repair damage in specific tissues caused by sepsis, such as the liver, lungs, kidneys, brain, and intestines. SCFA metabolites produced by probiotics have protective effects on cells by improving energy metabolism and cellular function. Probiotics can also reduce oxidative stress by increasing the activity of antioxidant enzymes, crucial in protecting tissues from damage caused by free radicals generated during sepsis.[15,18]

5. The Role of Probiotics in Combating Antibiotic Resistance

Bacteria can become resistant to antibiotics through various mechanisms, such as genetic mutations in genes coding for antibiotic targets. Activation of efflux pumps in bacterial cell walls can lead to the expulsion of antibiotics, making bacteria less sensitive or even resistant. Additionally, bacteria can produce enzymes that deactivate antibiotics, such as beta-lactamase, which breaks down the beta-lactam ring in beta-lactam antibiotics. This resistance mechanism becomes particularly concerning when these genes are located on transferable genetic elements like plasmids or transposons, allowing for the transfer of resistance genes to pathogenic bacteria, potentially making infections difficult to treat.[22]

The use of antibiotics, especially broad-spectrum ones, can also trigger gut dysbiosis, where beneficial bacteria are killed, and MDR pathogenic bacteria dominate. The administration of probiotics holds significant potential in combating infections caused by MDR bacteria. Probiotics can restore the balance of gut microbiota disrupted during antibiotic therapy, often triggering the growth of MDR pathogens.[23] Probiotics and their bioproducts serve as a promising approach, with the potential to prevent or reduce the severity of infections by antibiotic-resistant bacteria.[24] Additionally, a study showed that probiotic administration during antibiotic treatment can prevent negative side effects and complications like secondary infections resistant to antibiotics.[25]

Bacteriocins, one of the bioproducts produced by probiotics, have excellent potential in combating MDR pathogenic bacteria by acting as antimicrobial peptides that can directly damage the integrity of pathogenic bacterial cells. Bacteriocins, like nisin, work by forming pores in the target cell membrane, causing cell leakage. Certain bacteriocins can also bind to cell wall precursors and inhibit enzymes involved in cell wall formation. In addition, other bacteriocin abilities include inhibiting protein synthesis by interacting with ribosomes and inhibiting essential enzymes for cellular metabolism.[26,27]

Bacteriocins can also inhibit biofilm formation by acting as signaling peptides that disrupt intercellular communication known as quorum sensing. Generally, peptide-based quorum sensing in Gram-positive bacteria involves a two-component signal transduction system consisting of a histidine protein kinase (HPK) located on the cell membrane and a response regulator (RR) within the cell. This system is responsible for detecting signal peptides and inducing the appropriate cellular response.[26,27]

Bacteriocin activity against resistant bacteria can vary depending on the type of bacteriocin and the bacteria's resistance mechanisms. Bacteriocins have potential as an alternative to antibiotics, particularly in combating bacteria resistant to conventional antibiotics. However, some studies show pathogenic bacteria's resistance to bacteriocins through mechanisms such as modifying target receptors, producing proteases that degrade bacteriocins, or efflux pump mechanisms to expel bacteriocins from the cell. Some studies suggest that using bacteriocins in combination with antibiotics or other bacteriocins can increase effectiveness against resistant bacteria, as such combinations can overcome various resistance mechanisms and reduce the likelihood of bacteria developing further resistance. Overall, bacteriocins are still considered promising antimicrobial agents in the fight against antibiotic resistance, but further research is needed to fully understand their potential and limitations in clinical use.[28]

6. Conclusion

Probiotics demonstrate significant promise as a supplementary treatment in managing sepsis caused by multidrug-resistant (MDR) bacteria. They play a crucial role in modulating the equilibrium between proinflammatory and anti-inflammatory cytokines, potentially influencing the clinical management of sepsis. To ascertain the effectiveness of probiotics as adjunctive therapy in sepsis due to MDR bacteria, additional clinical research is essential.

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8. References

1. Nugraheni AY, Putri MS, Saputro AY. Evaluasi Ketepatan Antibiotik pada Pasien Sepsis. Pharmacon J Farm Indones. 2021;18(2):194–207.
2. Prasetyo DH, Purwanto B. Efek Probiotik pada Kadar IgA Mencit Model Sepsis. Maj Kedokt Bandung. 2010;42(4):175–80.
3. Indrayanto Y, Prasetyo DH. Efek Probiotik terhadap Mortalitas, Derajat Inflamasi Intestinal, dan Kadar IgA pada Mencit Model Sepsis. Maj Kedokt Bandung. 2013;45(1):10–5.
4. Khailova L, Frank DN, Dominguez JA, Wischmeyer PE. Probiotic administration reduces mortality and improves intestinal epithelial homeostasis in experimental sepsis. Anesthesiology. 2013;119(1):166–77.
5. Sari EK, Wihastuti TA, Ardiansyah W. Probiotik Meningkatkan Konsentrasi Hemoglobin Pada Tikus Putih Yang Diinduksi Lipopolisakarida Escherichia Coli. Maj Kesehat. 2018;5(1):18–25.
6. Marselina, Sumarny R, Arozal W, Rejeki MS. Evaluasi Penggunaan Antibiotik Definitif Pada Sepsis Neonatorum Awitan Dini Dan Lambat Di Rspad Gatot Soebroto. Maj Farm dan Farmakol. 2020;24(3):98–105.
7. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document: The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11(8):506–14.
8. Markowiak-Kopeć P, Śliżewska K. The effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome. Nutrients. 2020;12(4).
9. Latif A, Shehzad A, Niazi S, Zahid A, Ashraf W, Iqbal MW, et al. Probiotics: mechanism of action, health benefits and their application in food industries. Front Microbiol. 2023;14(August).
10. Monteagudo-Mera A, Rastall RA, Gibson GR, Charalampopoulos D, Chatzifragkou A. Adhesion mechanisms mediated by probiotics and prebiotics and their potential impact on human health. Appl Microbiol Biotechnol. 2019;103(16):6463–72.
11. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of Action of Probiotics. Adv Nutr. 2019;10:S49–66.
12. Dewi A sinta, Atifah Y, Farma SA, Yuniarti E, Fadhilla R. Pentingnya Konsumsi Probiotik untuk Saluran Pencernaan dan Kaitannya dengan Sistem Kekebalan Tubuh Manusia. Univ Negeri Padang. 2021;01(2021):149–56.
13. Mahesh R, Ilangovan P, Nongbri D, Suchiang K. Probiotics Interactions and the Modulation of Major Signalling Pathways in Host Model Organism Caenorhabditis elegans. Indian J Microbiol [Internet]. 2021;61(4):404–16. Available from: https://doi.org/10.1007/s12088-021-00961-3
14. Rabot S, Rafter J, Rijkers GT, Watzl B, Antoine JM. Guidance for substantiating the evidence for beneficial effects of probiotics: Impact of probiotics on digestive system metabolism. J Nutr [Internet]. 2010;140(3):677S-689S. Available from: https://doi.org/10.3945/jn.109.113738
15. Santos VR, Carvalho GO De, Silva BNF. Probiotics for the Management of Sepsis : Advances in Animal Models and Intensive Care Unit Environments. 2021;553–66.
16. Angurana SK, Bansal A, Singhi S, Aggarwal R, Jayashree M, Salaria M, et al. Evaluation of effect of probiotics on cytokine levels in critically Ill children with severe sepsis: A double-blind, placebo-controlled trial. Crit Care Med. 2018;46(10):1656–64.
17. Mazziotta C, Tognon M, Martini F, Torreggiani E, Rotondo JC. Probiotics Mechanism of Action on Immune Cells and Beneficial Effects on Human Health. Vol. 12, Cells. 2023. 1–33 p.
18. Ding L, Gong Y, Yang Z, Zou B, Liu X, Zhang B, et al. Lactobacillus rhamnosus GG Ameliorates Liver Injury and Hypoxic Hepatitis in Rat Model of CLP-Induced Sepsis. Dig Dis Sci [Internet]. 2019;64(10):2867–77. Available from: https://doi.org/10.1007/s10620-019-05628-0
19. Thomas CM, Versalovic J. Probiotic-host communication: Modulation of Host Signaling Pathways. Gut Microbes [Internet]. 2010;1(3):148–63. Available from: www.landesbioscience.com/journals/gutmicrobes/article/11712
20. Yılmaz M, Erdem AO. The protective role of probiotics in sepsis-induced rats. Ulus Travma ve Acil Cerrahi Derg. 2020;26(6):843–6.
21. Molina V, von Dessauer B, Rodrigo R, Carvajal C. Oxidative stress biomarkers in pediatric sepsis: a prospective observational pilot study. Redox Rep. 2017;22(6):330–7.
22. Ouwehand AC, Forssten S, Hibberd AA, Lyra A, Stahl B. Probiotic approach to prevent antibiotic resistance. Ann Med. 2016;48(4):246–55.
23. Newman A, Arshad M. The Role of Probiotics, Prebiotics, and Synbiotics in Combating Multidruf-Resistant Organisms. Clin Ther. 2020;42(9):1637–48.
24. Jain M, Stitt G, Son L, Enioutina EY. Probiotics and Their Bioproducts: A Promising Approach for Targeting Methicillin-Resistant Staphylococcus aureus and Vancomycin-Resistant Enterococcus. Microorganisms. 2023;11(10).
25. Wieërs G, Verbelen V, Van Den Driessche M, Melnik E, Vanheule G, Marot JC, et al. Do Probiotics During In-Hospital Antibiotic Treatment Prevent Colonization of Gut Microbiota With Multi-Drug-Resistant Bacteria? A Randomized Placebo-Controlled Trial

Comparing Saccharomyces to a Mixture of Lactobacillus, Bifidobacterium, and Saccharomyce. Front Public Heal. 2021;8(March):1–10.
26. Dobson A, Cotter PD, Paul Ross R, Hill C. Bacteriocin production: A probiotic trait? Appl Environ Microbiol. 2012;78(1):1–6.
27. Darbandi A, Asadi A, Mahdizade Ari M, Ohadi E, Talebi M, Halaj Zadeh M, et al. Bacteriocins: Properties and potential use as antimicrobials. J Clin Lab Anal. 2022;36(1):1–40.
28. Shavira A, Cahyadi AI, Windria S. Aktivitas Antibakteri dari Bakteriosin Lactobacillus spp. terhadap Bakteri Resistan. J Sain Vet. 2022;40(1):60.