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Lactobacillus johnsonii 6084 alleviated sepsis-induced organ injury by modulating gut microbiota

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Abstract

Sepsis is a public cause of death in intensive care unit patients. Probiotics were widely used to increase the survival rate of sepsis by a series of clinical research. The purpose of this research was to investigate the therapeutic effects of *Lactobacillus johnsonii* 6084 in septic mice. Sepsis mouse model was induced by LPS treatment. The influence of *L. johnsonii* 6084 on the protection of organ injury induced by sepsis was explored. Moreover, the composition of gut microbiota was studied to clarify the mechanism of *L. johnsonii* 6084 therapeutic effect on sepsis. *L. johnsonii* 6084 treatment could conspicuously decrease the mortality and organ injury of sepsis. The reduction of gut microbial diversity and richness in septic mice were moderated by the administration of 6084. The abundance of *Bacteroidetes* and *Proteobacteria* were change by LPS treatment while restored by *L. johnsonii* 6084. To conclude, probiotic 6084 may has optimistic result on reducing mortality of sepsis through rebalancing gut microbiota.

KEYWORDS

inflammation, Lactobacillus johnsonii 6084, microbiota, sepsis

1 | INTRODUCTION

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Fernando et al., 2018), is a general inflammatory illness with complex biological responses of body to various noxious stimuli, such as bacteria, virus which affects 5 million patients dead worldwide each year (Cecconi et al., 2018; Fleischmann et al., 2016; Kadri et al., 2017), which account for a main cause of death in intensive care units (ICU) worldwide (Rello et al., 2017). Although some therapies such as anti-infection, organ protection, and fluid resuscitation were used to ameliorate the symptoms of sepsis; however, the effective treatment strategies still have not been developed (Ferrer et al., 2014; Gu et al., 2015; Russell et al., 2017). Therefore, it is urgent to access new insights of the treatment for sepsis.

During sepsis, the composition of intestinal flora is severely distorted, with a loss of symbiotic bacteria and overgrowth of potentially pathogenic microorganisms (Kullberg et al., 2021). However, the gut microbiota lives in the digestive tracts of hosts, which is the body's first line to resistance against the invasion of external pathogens (Glenwright et al., 2017). The self-colonized intestinal microbial community is not only closely related to the digestion and absorption of nutrients but also plays a very important role in the regulation of the host's immune response (Han et al., 2020). Intestinal microbial disorders are closely related to many diseases, such as ulcerative colitis,

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inflammatory bowel disease (IBD), autoimmune disease, and sepsis (Paramsothy et al., 2017). Several studies have shown that sepsis could result in intestinal microbial disorders, which in turn exacerbate the development of sepsis (Adelman et al., 2020; Zaborin et al., 2014). The immunomodulatory properties of the gut microbiome provided a striking prospect for sepsis prevention and treatment. It is reported that a well-adjusted gut microbiota has a protecting role for inflammatory disease (Haak et al., 2018; Han et al., 2020). Thus, we hypothesized if restoring the balance of gut microbiota could have a protective effect on sepsis. There are many ways to restore disturbed gut microbes while probiotics are widely used.

Probiotics are live microbes that can have a valuable effect on hosts (Morelli & Capurso, 2012). Probiotics usually colonize at the intestinal tract of human or animal in a relatively stable amount which could interact with the host cells or intestinal microbiota to benefit human health, such as regulating the body's immune response (Lahner et al., 2016; Zou et al., 2020). It is reported that supplementation of probiotics could alleviate various inflammatory diseases by reconstructing the composition of intestinal microbiota (Tsui et al., 2021; Wang et al., 2021). Previous studies from our group have shown that oral supplementation of mice with probiotics significantly reduced inflammation induced by LPS (Han et al., 2020). Lactobacillus johnsonii, is one of the many microbes that exist in in the human intestine, is thought to be beneficial to human general health and well-being (Klaenhammer et al., 2007; Zhang et al., 2021). However, little is known of the valuable effects of L. johnsonii in improving sepsis. We hypothesized that L. johnsonii could protect organ injury caused by sepsis by regulating gut microbiota.

In the current study, we studied the effect of *L. johnsonii*, a main ingredient of yogurt, on septic mice, and explored the underlying mechanism. The expression levels of inflammatory factors and constitution of gut microbiota were examined to investigate the effect of *L. johnsonii* 6084. The results herein discussed suggest that *L. johnsonii* 6084 can protect visceral organs caused by sepsis through restoring gut microbiota. As such, diets supplemented with probiotics could alleviate organ damage caused by sepsis.

2 | MATERIALS AND METHODS

2.1 | Animals

Healthy male BALB/c mice used in this study (6-8 weeks old, average weight 20g) were obtained from the Experimental Animal Center of Air Force Medical University. The animal experiments protocols in this study followed the institutional guidelines agreed by the Ethics Committee of the Air Force Medical University.

2.2 | Bacteria and media

L. johnsonii 6048 were bought from China Center of Industrial Culture Collection. L. johnsonii 6084 were cultured in MRS medium growth medium supplemented with 1% lactose. Then, 100μ l of *L. johnso-nii* 6084 was added to 5-ml basal medium incubated at 180 rpm, at 37°C for 12 h which the final OD was 1. The CFU of *L. johnsonii* 6084 was determined by MRS agar medium.

2.3 | Animal model and L. johnsonii treatment

Septic mouse model was established through intraperitoneally injected with 1mg/kg LPS (Sigma-Aldrich) at the beginning of experiment, with a second dose administered 4 days after the first injection. Mice were randomized into four groups (n = 8 per group): Control group (mice were intragastrically administered only with 300 µl/day PBS for 1 week); LPS group (mice were administered with PBS after LPS administration); LPS+L. johnsonii 6084 group (mice were intragastrically administered with L. johnsonii 6084 for 1 week after LPS administration); L. johnsonii 6084 group (mice were intragastrically administered with L. johnsonii 6084 for 1 week without LPS administration). Mice were intragastrically administered with 300 µl/day L. johnsonii 6084 (1×10⁹ CFU/ml) or 300 µl/day PBS once every other day. The concentration of LPS increased to 15 mg/kg when monitor the survival rate (n = 10 per group). Mice were anesthetized with isoflurane after treatment 3 days (the total treatment time was 1 week). Blood in mice was obtained by cardiac blood collection under anesthesia. Then, the lung, small intestine, liver, and kidney tissues were collected and divided into two parts. Feces were obtained from cecum and stored at liquid nitrogen for gut microbiota analysis.

2.4 | Weight and sampling

Body weight of mice was recorded for all groups. The serum and tissues were collected after LPS treatment 1 week. Fresh colon samples from all groups were collected and immediately frozen using liquid nitrogen for further Microbial DNA extraction and Illumina MiSeq sequencing.

2.5 | Enzyme-linked immunosorbent assay (ELISA)

Blood was collected from the left ventricle of all group mice. The concentrations of Interleukin-1 β (IL-1 β) and tumor necrosis factor α (TNF- α) in serums were examined using ELISA kits (Jiancheng).

2.6 | Hematoxylin and Eosin (H&E) Staining

Tissues (Liver, Kidney, Lung, and Gut) were fixed in 4% paraformaldehyde, dehydrated in alcohol, and embedded in paraffin. The samples were cut into 4-µm thick sections and deparaffinized and stained with hematoxylin and eosin (H&E) for histological analysis.

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2.7 | RNA isolation and quantitative real-time PCR

Total RNA from tissues was extracted using TRIzol methods (Invitrogen) and reversely transcribed into cDNA through PrimeScript[™] RT Kit (Takara). SYBR® PremixEx Taq[™] II and Bio-Rad CFX system were used to analyze the expression of genes. Quantitative RT-PCR data were determined based on cycle threshold (Ct) and normalized to internal loading control genes GAPDH. The primers sequences are listed in Table 1.

2.8 | DNA extraction and MiSeq sequencing

E.Z.N.A.® Stool DNA Kit was used to extract bacterial DNA (Omega BioTek) following the manufacturer's instructions. The DNA samples were assessed by PCR with the primer (27F/1492R) targeting the 16S rRNA gene. The purity and quality of the DNA samples were examined using 1% agarose gels containing ethidium bromide and then the DNA samples were sent for MiSeq sequencing.

MiSeq sequencing was used to analysis the structure of gut microbiota (Genergy Biotech, Shanghai, China) targeting the V3-V4 region of the bacterial 16S rRNA gene using primers 341F (5'-CCTACGGGNGGCWGCAG-3') and 785R (5'-GACTACHVGGGTATCTAATCC-3'). We used the Sequence Read Archive (SRA) database to deposit raw reads. Operational taxonomic units (OTUs) were clustered with a 97% similarity cutoff using UPARSE. UCHIME was used to identify and remove chimeric sequences. RDP classifier against the SILVA (SSU123) 16S rRNA database using a confidence threshold of 70% was used to analyze the taxonomy of each 16S rRNA gene sequence.

2.9 | Statistical analysis

Data are presented as $mean \pm SD$. Student's t-test was used to determine the statistical differences among two groups, whereas one-way analysis of variance (ANOVA) was used for comparisons between multiple groups. p value less than .05 was considered statistically significant. GraphPad Prism 6.0 was used for analyses. For gut microbiota analyses, Wilcoxon test was used for two independent samples while Kruskal-Wallis test was applied for inter group analysis.

3 | RESULTS

3.1 | *L. johnsonii* 6084 reduced the mortality and inflammation in septic mice

We first evaluated the effect of *L. johnsonii* 6084 on septic mice. Mice subjected to LPS had an approximately 20% 7-day survival rate, and the survival rate was obviously higher in septic mice treated with *L. johnsonii* 6084 compared with that in the LPS group (50%) (Figure 1a). Consistent with the reduced mortality rate, *L. johnsonii* 6084 treatment significantly decreased the expression of serum inflammatory cytokines, IL-1 β , and TNF- α , in septic mice (Figure 1b). We further examined the levels of inflammatory cytokines in lungs, livers, kidneys, and intestines. Mice subjected to LPS had a much higher expression of IL-1 β , TNF- α , and IL-6 in all tissues while *L. johnsonii* 6084 treatment substantially decreased the inflammatory cytokines (IL-1 β , TNF- α , and IL-6) expression in all tissues compared with those in the LPS group (Figure 1c). These results suggested that *L. johnsonii* 6084 treatment could reduce the mortality and inflammation in LPS-induced septic mice.

3.2 | *L. johnsonii* 6084 treatment protected against the organ injuries in septic mice

We further verified the effect of L. johnsonii 6084 on organ injuries induced by sepsis. Mice subjected to LPS had a much higher levels of Cr, BUN, ALT, and AST than those in control group while L. johnsonii 6084 treatment substantially decreased the levels of Cr, BUN, ALT, and AST compared with those in LPS group (Figure 2a). Moreover, H&E staining revealed that organ injuries induced by sepsis were mitigated with L. johnsonii 6084 treatment. As shown in Figure 2b, in pulmonary sections, the lung tissue from the septic mice treated with L. johnsonii 6084 showed remarkable decreased infiltration of inflammatory cells, alleviated edema and hemorrhage, and less damage of alveolar structures compared with those in LPS group. In liver sections, the liver section from the septic mice treated with L. johnsonii 6084 had relieved congestion of veins as well as hepatocyte necrosis compared with those in the LPS group. In the kidney section from the septic mice treated with L. johnsonii 6084, there were less necrotic glomeruli and the tubule structure was nearly normal compared with those in the LPS group. In the intestines section from the septic mice treated with L. johnsonii 6084, alleviated shortened intestinal villi and

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Names	Species	Sense	Antisense
IL-1β	Mouse	CAACCAACAAGTGATATTCTCCATG	GATCCACACTCTCCAGCTGCA
TNF-α	Mouse	TATGGCCCAGACCCTCACA	GGAGTAGACAAGGTACAACCCATC
IL-6	Mouse	CAACGATGATGCACTTGCAGA	CTCCAGGTAGCTATGGTACTCCAGA
MCP-1	Mouse	AGCAGCAGGTGTCCCAAAGA	GTGCTGAAGACCTTAGGGCAGA
GAPDH	Mouse	TGTGTCCGTCGTGGATCTGA	TTGCTGTTGAAGTCGCAGGAG



FIGURE 1 *L. johnsonii* 6084 alleviates the inflammation caused by LPS-induced sepsis. (a) Survival rates of mice with or without *L. johnsonii* 6084 treatment (n = 10). (b) The concentration of IL-1 β and TNF- α in blood were determined using commercial ELISA kits (n = 8). (c) *L. johnsonii* 6084 intervention resulted in decreased inflammation of gut, lung, liver, and kidney (n = 8). Error bars represent SEM. * p < .05 compared with control group. # p < .05 compared with LPS group.

FIGURE 2 *L. johnsonii* 6084 protected against organ injuries caused by sepsis. (a) *L. johnsonii* 6084 interference resulted in decreased Cr, BUN, ALT, and AST (n = 8). (b) H&E staining of lung, liver, gut, and kidney tissues from different groups. Sections were examined and photographed under a microscope (n = 8). * p < .05 compared with control group. # p < .05 compared with LPS group.



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less infiltration of inflammatory cells were observed compared with those in the LPS group. These results evidenced that *L. johnsonii* 6084 treatment protected against organ injuries in LPS-induced septic mice. 6084 treatment increased microbial diversity and richness in LPSinduced septic mice Figure 3.

3.3 | *L. johnsonii* 6084 treatment increased microbial diversity and richness in LPS-induced septic mice

We performed 16S rDNA gene amplicon sequencing to detect change of the community structure of gut microbiota. We found that Shannon index (represent the diversity of gut microbiota) and Chaos 1 index (represent the richness of gut microbiota) were significantly reduced in septic mice. With the treatment of *L. johnsonii* 6084, both the indexes increased in septic mice, which reached a level closer to that of the control group. These results suggested that *L. johnsonii*

3.4 | Administration of *L. johnsonii* 6084 altered the intestinal microbiota composition

Nine phyla were detected in microbial profiles of experimental mouse (Figure 4a), among which *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, and *Deferribacteres* were the four major phyla in septic mice, whereas, *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Deferribacteres* were the four major phyla in the samples of control group mice. *L. johnsonii* 6084 treatment changed the abundance of gut microbiota. The intestines microbiota composition was also analyzed at genus levels (Figure 4b).





Sample



FIGURE 4 The relative abundances of gut microbiota at family level (a) and genus (b) levels in control, LPS, L. johnsonii 6084, and L. johnsonii 6084 + septic mice



FIGURE 5 *L. johnsonii* 6084 has a significant impact on microbiota composition (n = 8). (a) The change of gut microbiota at phylum level. (b) The change of gut microbiota at genus level.

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The differences between gut microbiota of the four groups of mice at the family and genus levels are presented in Figure 5. The relative abundance of *Bacteroidetes* and *Proteobacteria* was significantly different in four groups among all identified phylum (p = .0016). *Bacteroidetes* in LPS mouse was significantly increased and *L. johnsonii* 6084 administration decreased dramatically while *Proteobacteria* exhibited an opposite trend (Figure 5a).

Most of the microbiota at a genus level were dominated by unclassified Lachnospiraceae, Helicobacter, Barnesiella, Alistipes, and Clostridium XIVb while there was two exception LPS-treated mouse which was dominated by Bacteroides. The relative abundance of Bacteroides, Barnesiella, Bilophila, Eubacterium, Flavonifractor, Helicobacter, Klebsiella, Oscillibacter, Turicibacter, unclassified Bacteroidales, unclassified Clostridiaceae, unclassified Porphyromonadaceae, and unclassified Prevotellaceae were markedly different in four groups at genera level. Bacteroides, Barnesiella, Eubacterium, Flavonifractor, Klebsiella, unclassified Porphyromonadaceae, and unclassified Porphyromonadaceae significantly increased after LPS treatment and its abundance decreased after L. johnsonii 6084 administration while Helicobacter, Oscillibacter, unclassified Bacteroidales, and unclassified Clostridiaceae exposed an opposite trend (Figure 5b). Linear discriminant analysis effect size (LEfSe) was used to determine the differentially abundant features of the four groups which is an algorithm for characterizing genomic features most likely to explain differences between groups. *Bacteroidetes Deltaproteobacteria*, *Gammaproteobacteria*, and *Erysipelotrichia* may be regarded as the key responders of the oral administration of strain 6084 on normal and LPS-treated mice (Figure 6).

4 | DISCUSSION

In our study, we investigated the effect of *L. johnsonii* 6084 on the inflammation and organ injury in LPS-induced septic mice and it was evidenced that *L. johnsonii* 6084 treatment could reduce the mortality and inflammation and protect against the organ injuries in LPS-induced septic mice, which might result from the alteration of gut microbiota pattern.

Sepsis often causes a systemic inflammatory response. Alleviating patients' inflammatory response is an effective way to relieve the symptoms of sepsis (Bai et al., 2018). Many probiotics



FIGURE 6 Linear discriminant analysis effect size analyzed the differentially abundant features in different groups. The cladograms represented indicate the bacterial taxa are obviously different among the four groups. This analysis helps to identify a first selection of differential bacterial taxa in the considered groups.

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can reduce the inflammatory response (Khalique et al., 2019; Yang et al., 2020). Probiotics are microorganisms that colonize the intestinal tract, which can inhibit the growth of harmful bacteria and maintain a stable environment in the intestinal tract. In recent years, it has been found that probiotics have been widely used in clinical practice such as ulcerative colitis, Crohn's disease, intestinal tumors, and other diseases (Jakubczyk et al., 2020). Meanwhile, a large number of clinical and basic studies have confirmed that probiotics have a definite effect on sepsis(Chen et al., 2020; Tsui et al., 2021). Therefore, probiotics are potential candidates for decreasing the symptoms of sepsis. L. johnsonii are probiotics that have been used to treat many illnesses. For instance, L. johnsonii BS15 can attenuate inflammation in obese mice (Xin et al., 2014); L. johnsonii La1 can be useful in preventing bacterial translocation in cirrhosis (Soriano et al., 2012). L. johnsonii BS15 intake benefits the neuroinflammation and demyelination in the hippocampus (Xin et al., 2020). Similarly, we observed that L. johnsonii decreased the level of inflammatory factors in an LPS-induced sepsis mouse model.

Various studies reported that the gut microenvironment and the flora composition of sepsis patients were changed significantly (Chen, 2020; Kullberg et al., 2021). During sepsis, the local immune system of the gut was imbalanced, and the gut flora were overproduced, producing a large number of metabolites and toxins, resulting in the damage of intestinal mucosal barrier. The damage of intestinal mucosal barrier will further promote the translocation of intestinal flora and further aggravate sepsis. Previous studies showed shifts in the Firmicutes to Bacteroidetes ratio of septic mice, as well as reduced microbiota diversity (Ojima et al., 2016; Zaborin et al., 2014). In the present study, the microbiota diversity presented significant differences among groups. Repairing gut microbiota of sepsis provides a new idea for the treatment of it. One of the important ways that probiotics treat diseases is to change the composition of gut microbes (Teixeira et al., 2021; Yin et al., 2021). In this study, the composition of gut microbiota was changed after LPS treatment while it was restored by L. johnsonii 6084 treatment especially the relative abundance of Bacteroides, Barnesiella, Flavonifractor, etc. The results indicated that L. johnsonii 6084 protects against the organ injuries caused by sepsis through restoring the composition of gut microbiota.

In summary, we demonstrated that *L. johnsonii* 6084 can alleviate inflammation in vitro. It reduced the levels of inflammatory factors caused by sepsis, which may through resistance some pathogenic bacteria enriched in the gut after intraperitoneal injection of LPS promote higher intestinal permeability, and alter the composition of the gut microbiota. *L. johnsonii* 6084 may be used to treat other systemic inflammatory diseases, such as inflammatory bowel disease, systemic inflammatory arthritis, and multiple sclerosis. In our previous study, we found that *S. thermophilus* 19 has the same ability of *L. johnsonii* 6084. Most of the research focused on the therapeutic potential of single probiotics while we can aim to study the efficacy of multiple probiotics in the future. We will investigate the therapeutic potential of the combination of *S. thermophilus* 19 and *L. johnsonii* 6084. Collectively, the results of our study provide a conceptual

framework to further text this hypothesis in humans to treat sepsis and other systemic inflammatory diseases.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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