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Probiotic Lactobacillus plantarum IS-10506, Expression of Glial Fibrillary Acidic Protein and Platelet Endothelial Cell Adhesion Molecule-1 by Astrocytes and Endothelial Integrity: The Importance of Intestinal Microbiota as Blood Brain-Barrier Stabilizer

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Gut microbiota is a complex community that helps maintain the dynamic metabolic ecological balance of the brain through the gut–brain axis and keeps the blood–brain barrier structure intact. However, the knowledge of how the gut microbiota responds to xenogenous influences on the blood–brain barrier structure remains limited. This study hypothesizes that probiotic Lactobacillus plantarum IS 10506 supplementations could ameliorate the disruption of the blood–brain barrier structure. To this end, we examined effect of the probiotic L. plantarum IS 10506 on the expression of glial fibrillary acidic protein and platelet endothelial cell adhesion molecule-1 in the control and E. coli serotype O55:B5 lipopolysaccharide treated blood–brain barrier disruption model of Wistar rats. The rats receiving L. plantarum IS 10506 alone or along with E. coli serotype O55:B5 lipopolysaccharide exhibited upregulation of the expression of glial fibrillary acidic protein and platelet endothelial cell adhesion molecule-1. In conclusion, the probiotic L. plantarum IS-10506 stimulates the restoration of blood–brain barrier disruption.

Keywords: Blood–brain barrier, Brain injury, Glial fibrillary acidic protein, Gut microbiota, Lactobacillus plantarum IS-10506, Platelet endothelial cell adhesion molecule-1, Probiotic

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INTRODUCTION

The blood–brain barrier (BBB) functions as a gatekeeper to control the passage and exchange of molecules and nutrients between the circulatory system and the brain parenchyma. It is essential as a physical barrier for maintaining a precisely regulated intracerebral microenvironment, ensuring homeostasis of the central nervous system (CNS) to brain development and function (Banks et al., 2015; Moretti et al., 2015; Wimmer et al., 2019). BBB characteristics limit paracellular diffusion while allowing larger molecules’ tightly controlled receptor-mediated endocytosis and the transporter-mediated intake of smaller nutrients such as glucose, insulin, and iron. Endothelial cells interact closely with other CNS cells such as neurons, pericytes, and astrocytes, through adherent junctions, influx and efflux transporters, metabolic enzymes, and extracellular matrix (Abbott et al., 2006; Sharif et al., 2018; Sofroniew and Vinters, 2010). Breakdown of the BBB and increased immune cell trafficking into the CNS are hallmarks of the pathogenesis of many CNS diseases (Banks et al., 2015; Sharif et al., 2018).

Gut microbiota is a complex community that helps maintain dynamic metabolic ecological balance and keep the BBB...
structure intact. The normal structure of the BBB is essential as defender brain functions from external intruders to the CNS (Bransiet al., 2014; Logsdon et al., 2018; Varatharaj and Galea, 2017). Glial fibrillary acidic protein (GFAP) of astrocytes is a vital player in the complex cascade of cellular adaptations taking place in the CNS in response to injury and disease (Mandyam et al., 2017; Parker et al., 2020; Winger et al., 2014). Platelet endothelial cell adhesion molecule-1 (PECAM-1; CD31) is an essential factor for supporting the BBB, expressed on vascular compartment cells, and regulated vascular integrity and immune cell trafficking (Wimmer et al., 2019).

The knowledge of how gut microbiota affects the GFAP of astrocyte and PECAM-1 of the BBB regulation as a response to exogenous influence remains limited. The present study investigated whether the probiotic Lactobacillus plantarum 15 strain 10506, prevalent in Indonesia and a typical intestinal resident, can influence the BBB.

MATERIAL AND METHODS

Animals
Thirty-six male, 12-weeks old, Wistar rats weighing 100–120 g were procured from the central animal facility of the Cellular and Molecular Biology Laboratory, Faculty of Science, Brawijaya University, Malang, Indonesia. All the rats were given water and a standard pellet diet containing 20–25% protein, 5–12% fat, 2.5% fiber, and 45–60% carbohydrate ad libitum. After 14 days of acclimatization, the rats were divided into four groups of nine rats per group as follows:

Group K1: Treated with distilled water daily through gavage
Group K2: Treated with 2.5 mg/kg lipopolysaccharide (LPS) derived from the E. coli serotype O55:B5 through gavage on the first day, then treated with distilled water daily for 13 additional days
Group K3: Treated with 2.5 mg/kg LPS derived from the E. coli serotype O55:B5 through gavage on the first day, then treated with 2.5 mL of 2.67 × 10⁶ CFU/mL L. plantarum 15 strain 10506 daily for 7 following days
Group K4: Treated with 2.5 mg/kg LPS derived from the E. coli serotype O55:B5 through gavage on the first day, then treated with 2.5 mL of 2.67 × 10⁶ CFU/mL L. plantarum 15 strain 10506 daily for 13 following days.

The probiotic used was from freeze-dried powder of L. plantarum 15 strain 10506 (GenBank accession No. DC680149). The rats were examined and weighed daily. At the end of the experiment, day 14, the brain tissue was dissected. The study reported herein received ethical approval from the Animal Care and Use Committee at the Faculty of Veterinary Medicine, Brawijaya University, Malang, Indonesia (KEP:100-KEP-UB-2000).

Probiotic Supplementation
Microencapsulated L. plantarum strain 10506 (GenBank accession No. DQ860148) was packed in an aluminum foil sachet at the Pharmacy Installation of Dr. Soetomo Hospital (Surabaya, Indonesia) and dissolved in 1.5 mL sterile water and administered to the rats via a gastric tube once daily for 7 days at a dose of 2.67 × 10⁶ CFU/day. Probiotic viability was assessed 1 week prior to the treatment.

LPS
For LPS dose–response and time studies, the male Wistar rats were weighed and given an intraperitoneal injection of 3 mg/kg LPS. The LPS was derived from the E. coli serotype O55:B5 (Cat. No. L5418, Sigma-Aldrich, St. Louis, MO, USA) dissolved in sterile normal saline.

Immunohistochemistry
The brain tissues were fixed in 10% formalin solution, followed by dehydration and paraffin embedding. Serial sections of the tissues were cleaned and fixed in 10% formalin buffer solution. Then, this procedure is followed by dehydration, clearing, and embedding. The tissue sections were probed with antibodies against the GFAP (Cat. No. sc-36673, Sigma-Aldrich, St. Louis, MO, USA) of astrocyte and PECAM-CD31 (Cat. No. sc-376784, Sigma-Aldrich, St. Louis, MO, USA). The sections were observed under a light microscope (CX21; Olympus, Tokyo, Japan) and photographed with an ILCE6000 camera (Sony, Tokyo, Japan). The number of immunopositive cells in 20 random fields at 100X and 400X magnification was counted.

RESULTS

The microscope visualization of the BBB structure and the results of the normal structure can be seen in Figure 1 for the control group of brain GFAP of astrocyte expression (brown color). The GFAP manifestation of the astrocyte expression group after being exposed by the LPS was shown in Figure 2. There was an improvement of the brain GFAP in the astrocyte expression group (brown color) after being treated by L. plantarum 15 strain 10506 for 7 days (Fig. 3). However, L. plantarum 15 strain 10506 treatment for 14 days showed a better result than 7 days, proven by the increased expression of GFAP of the astrocyte. (Fig. 4). The normal structure of the PECAM-1 in rats (brown color) as the control group was provided in Figure 5. The manifestation of the PECAM-1 expression after the LPS treatment was shown in Figure 6 and the black arrow showed the downregulation of the PECAM-1 expression. The result of this study confirmed that the probiotic L. plantarum 15 strain 10506, treated for 7 days as a model of gut microbiota, improved (black arrow) disruption of PECAM-1 expression (Fig. 7). The long treatment period of 14 days also showed upregulation of the PECAM-1 expression (Fig. 8).

DISCUSSION

Gut microbiota is a complex community composed of trillions of microbes that perform several tasks which are essential to our healthy physiology and help to maintain dynamic metabolic and ecological balance and keep the structure of the BBB intact (Caspari et al., 2019; Gomes et al., 1999; Hol and Pekny, 2015; Varatharaj and Galea, 2017). Many studies using the probiotic L. plantarum
FIGURE 1 | Representative image of control group of brain glial fibrillary acidic protein (GFAP) of astrocyte expression (brown color in black arrow) in rats (100X magnification - L and 400X magnification - R); 1 bar = 0.01 mm.

FIGURE 2 | Representative image of disruption brain GFAP of astrocyte expression (disappeared brown color in black arrow) on lipopolysaccharide group in rats (100X magnification - L and 400X magnification - R); 1 bar = 0.01 mm.

FIGURE 3 | Representative image of recovery brain GFAP of astrocyte expression (appearance of brown color in black arrow) in rats treated with Lactobacillus plantarum IS 10506 (7 days) in rats (100X magnification - L and 400X magnification - R); 1 bar = 0.01 mm.

FIGURE 4 | Representative image of recovery brain GFAP of astrocyte expression (appearance clearer brown color in black arrow) treated with L. plantarum IS 15608 (14 days) in rats (100X magnification - L and 400X magnification - R); 1 bar = 0.01 mm.
**FIGURE 5** | Representative image of control group of brain CD31 (platelet endothelial cell adhesion molecule-1 [PECAM-1]) expression [brown color in black arrow] in rats (100X magnification – L and 400X magnification – R); 1 bar = 0.01 mm.

**FIGURE 6** | Representative image of brain CD31 PECAM-1 expression [disappeared brown color in black arrow] on LPS group in rats (100X magnification – L and 400X magnification – R); 1 bar = 0.01 mm.

**FIGURE 7** | Representative image of brain CD31 PECAM-1 expression [appearance of brown color in black arrow] treated with *L. plantarum* IS 10506 (7 days) in rats (100X magnification – L and 400X magnification – R); 1 bar = 0.01 mm.

**FIGURE 8** | Representative image of brain CD31 PECAM-1 expression [appearance of brown color in black arrow] on *L. plantarum* IS 10506 (14 days) in rats (100X magnification – L and 400X magnification – R); 1 bar = 0.01 mm.
Other studies report that other gut microbiota such as *Clostridium butyricum*, *C. tyrobutyricum*, and *Bacteroides thetaiotaomicron* impact the BBB integrity. These microbial-derived metabolites have essential metabolic and signaling functions, which can modulate host homeostasis, including the BBB integrity and brain function (Parker et al., 2020). These results proved the potential of gut microbes as modulators of the BBB integrity for brain health.

**CONCLUSION**

This study indicates that *L. plantarum* IS-10506 shore up the BBB to improve the GFAP and PECAM-1 expression as a stimulator for restoring the BBB disruption. These findings suggest that probiotics potentially promote brain defense and offer the model for investigating the effects of gut microbiota on the BBB to prevent exogenous pathogens on the CNS infections.

**CONFLICT OF INTEREST DECLARATION**

The authors state that there are no conflicts of interest to disclose.

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