



Article

Suppressive Effects of *Lactobacillus* on Depression through Regulating the Gut Microbiota and Metabolites in C57BL/6J Mice Induced by Ampicillin

Wan-Hua Tsai ¹, Wen-Ling Yeh ¹, Chia-Hsuan Chou ¹, Chia-Lin Wu ² , Chih-Ho Lai ^{3,4,5} , Yao-Tsung Yeh ⁶ , Chong-An Liao ⁶ and Chih-Chung Wu ^{7,*}

- ¹ Research and Development Department, GenMont Biotech Incorporation, Tainan 74144, Taiwan
² Department of Biochemistry, College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan
³ Department of Microbiology and Immunology, College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan
⁴ Department of Nursing, Asia University, Taichung 413305, Taiwan
⁵ Department of Medical Research, School of Medicine, China Medical University and Hospital, Taichung 404333, Taiwan
⁶ Aging and Diseases Prevention Research Center, Fooyin University, Kaohsiung 83102, Taiwan
⁷ Department of Food and Nutrition, Providence University, Taichung 43301, Taiwan
* Correspondence: ccwumail@pu.edu.tw; Tel.: +886-4-26328001 (ext. 18318)

Abstract: Depression is a medical and social problem. Multiple metabolites and neuroinflammation regulate it. Modifying the gut microbiota with probiotics to reduce depression through the gut-brain axis is a potential treatment strategy. In this study, three anti-depressive potentials of *Lactobacillus* spp. (LAB), including *L. rhamnosus* GMNL-74, *L. acidophilus* GMNL-185 and *L. plantarum* GMNL-141, which combined to produce low dosage LAB (1.6×10^8 CFU/mouse, LABL) and high dosage LAB (4.8×10^8 CFU/mouse, LABH), were administered to C57BL/6 mice induced depression by ampicillin (Amp). A behavioral test of depression, 16S ribosomal RNA gene amplicon sequencing, bioinformatic analysis, and short-chain fatty acid (SCFA) content measurement were executed to investigate the gut microbiota composition, activation of nutrient metabolism pathways, levels of inflammatory factors, gut-derived 5-HT biosynthesis genes, and SCFA levels in C57BL/6 mice. Results showed that after mice were induced by Amp, both LAB groups recovered from depressive behaviors, decreased the abundance of *Firmicutes*, and increased the abundance of *Actinobacteria* and *Bacteroidetes* in the mouse ileum. The prediction of metabolism pathways of microbes revealed the activation of arginine and proline metabolism, cyanoamino acid metabolism, and nicotinate and nicotinamide metabolism were increased, and fatty acid synthesis was decreased in both LAB groups. The LABH groups showed increased levels of acetic acid, propanoic acid, and iso-butyric acid and decreased butyric acid levels in the cecum. LABH treatment increased claudin-5 and reduced IL-6 mRNA expression. Both LAB groups also reduced monoamine oxidase, and the LABH group increased vascular endothelial growth factor mRNA expression. These results showed that the composite of three LAB exerts antidepressant effects by regulating the gut microbiota and modifying the levels of depression-related metabolites in C57BL/6J Amp-treated mice.

Keywords: *Lactobacillus*; gut microbiota; depression-related metabolites; C57BL/6J mice



Citation: Tsai, W.-H.; Yeh, W.-L.; Chou, C.-H.; Wu, C.-L.; Lai, C.-H.; Yeh, Y.-T.; Liao, C.-A.; Wu, C.-C. Suppressive Effects of *Lactobacillus* on Depression through Regulating the Gut Microbiota and Metabolites in C57BL/6J Mice Induced by Ampicillin. *Biomedicines* **2023**, *11*, 1068. <https://doi.org/10.3390/biomedicines11041068>

Academic Editor: Ryota Niikura

Received: 26 February 2023

Revised: 15 March 2023

Accepted: 24 March 2023

Published: 1 April 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

There are almost 100 trillion bacteria living in the human intestine [1]. Previous studies showed that gut microbiota has many physiological effects that include improvement in the treatment of different CVDs [2], regulate body weight change [3], and modulate the immune response [4], especially in intestinal inflammation [5]. The diverse gut microbiota predominantly comprises bacteria from three important phyla: *Firmicutes*, *Bacteroidetes*,