Al-Jahiz: Journal of Biology Education Research
ISSN 2722-5070 (Print) ISSN 2722-5275 (Online)
Vol. 6 No. 2 July-December 2025
Available online at:
http://e-journal.metrouniv.ac.id/index.php/Al-Jahiz

Immunomodulatory Effects of Synbiotics Lactic Acid Bacteria from Dangke and Inulin from Dahlia Tubers

Ayu Febriani[1], Hafsan[2]*, Fatmawati Nur[3], Cut Muthiadin[4], Faten Khudaer[5]
[1]Hasanuddin University
Jl. Perintis Kemerdekaan Km 10, Tamalanrea, Makassar, South Sulawesi, Indonesia
[2,3,4]Universitas Islam Negeri Alauddin
Jl. H. M Yasin Limpo No.36, Romangpolong, Somba Opu, Gowa, South Sulawesi, Indonesia
[5]Al-Manara College for Medical Sciences
V43Q+RFC, Amarah, Maysan Governorate, Iraq
*Corresponding author: hafsan.bio@uin-alauddin.ac.id

Article Information

Article History:
Received: March 23, 2025
Revised: May 19, 2025
Published: October 18, 2025

Keywords:
Synbiotics, *Lactobacillus fermentum,* Dangke, inulin, immunomodulation.

ABSTRACT

Synbiotics, the synergistic combination of probiotics and prebiotics, have attracted growing scientific interest due to their potential to modulate immune responses. However, the immunomodulatory effects of synbiotics derived from traditional foods remain underexplored. This study aimed to evaluate the immune-enhancing potential of synbiotics formulated from *Lactobacillus fermentum* isolated from Dangke (a traditional South Sulawesi cheese) and inulin extracted from Dahlia tubers. The novelty of this work lies in the utilization of culturally unique, locally sourced microbial and prebiotic components that have not previously been tested for immunological impact. A total of 28 mice were randomly divided into four groups: one negative control group (P0) and three treatment groups (P1, P2, P3) receiving different doses of synbiotics over a 20-day treatment period. Parameters observed included changes in body weight, macrophage phagocytosis activity, and organ indices (liver and spleen). Results showed that mice in P1 and P2 groups exhibited significant increases in body weight (P1: +12.5%, P2: +15.3%, $p < 0.05$) compared to the control. Moreover, macrophage phagocytic activity was markedly improved in the treatment groups ($p < 0.01$). Liver and spleen indices were also significantly elevated ($p < 0.05$), indicating enhanced organ function. These findings suggest that synbiotics containing *L. fermentum* and Dahlia inulin have promising immunomodulatory effects, highlighting their potential for development as novel functional food ingredients with health-promoting benefits.

How to Cite: Febriani, A., Hafsan, Nur, F., Muthiadin, C., & Khudaer, F. (2025). Immunomodulatory Effects of Synbiotics Lactic Acid Bacteria from Dangke and Inulin from Dahlia Tubers. *Al Jahiz: Journal of Biology Education Research*. 6(2), 1–14. DOI: https://doi.org/10.32332/al-jahiz.v6i2.10393.

Published by: Al-Jahiz: Journal of Biology Education Research
Website: https://e-journal.metrouniv.ac.id/index.php/Al-Jahiz/index

INTRODUCTION

Dangke, a traditional milk coagulation product from South Sulawesi, has long been recognized locally for its nutritional benefits (Mustamin, S. F. et al., 2022; Nur, 2012; Rahman et al., 2023). In recent years, there has been growing interest in the potential probiotic properties of lactic acid bacteria (LAB) found within it (Al-Fataftah et al., 2013). Probiotics are live microorganisms that, when consumed in adequate amounts, provide health benefits to the host, particularly through enhancing digestive health and modulating the immune system (Hill et al., 2014). However, comprehensive research on the immunomodulatory potential of LAB from Dangke remains limited.

Inulin from dahlia tubers is a prebiotic, a food component that is indigestible by humans but metabolized by gut microbiota, supporting the growth and activity of beneficial bacteria (Slavin, 2013). The combination of probiotics and prebiotics is known as synbiotics, expected to provide greater health benefits compared to their separate use (Markowiak & Śliżewska, 2017). Recent studies indicate that synbiotics play a significant role in modulating the immune system, particularly in enhancing the body's immune response to pathogens and reducing inflammation (Kechagia et al., 2013). With the increasing prevalence of immune-related diseases such as allergies, autoimmune diseases, and chronic infections (Askari et al., 2021; Balta et al., 2021; Yadav et al., 2022), finding safe and natural solutions to enhance immune function is crucial.

Current research gaps lie in the limited exploration of the potential synbiotics derived from Dangke and inulin from dahlia tubers. Previous studies have predominantly focused on LAB from commercial fermented dairy products and prebiotics from more common sources like chicory (Saad et al., 2013). Therefore, this study aims to address this gap by evaluating the immunomodulatory effects of a synbiotics combination of LAB from Dangke and inulin from Dahlia tubers.

Research by (Goyal, S., Sharma, K., & Ajeet, 2015) demonstrated that prebiotics can increase the levels of *Bifidobacteria* and *Lactobacilli* in the gut, associated with improved immune function. Similarly, studies by (Azad et al., 2018) indicated that the use of synbiotics can enhance cellular and humoral immune responses. However, these studies utilized commercial prebiotics and probiotics, whereas the potential of synbiotics from local sources such as Dangke and inulin from dahlia tubers remains largely unexplored.

This research is relevant as it leverages local resources with potential significant health benefits (Mustamin, S. F. et al., 2022; Rahman et al., 2023). Dangke, as a source of LAB, holds high probiotic potential due to its unique traditional fermentation method, which can produce LAB strains with distinct immunomodulatory properties (Burhan et al., 2017; Djide et al., 2021; Nur, 2012)). Additionally, dahlia tubers rich in inulin are readily accessible and can be used to enhance local community health through a synbiotics approach (Abdurrahman et al., 2016; Kusmiyati et al., 2018).

Studies on synbiotics from local sources also carry positive economic and ecological implications (Dahiya & Nigam, 2022). The production and utilization of local ingredients can reduce dependency on imported products, support the local economy, and decrease carbon footprints associated with food transportation (Hutkins et al., 2016). Furthermore, the success of this research could pave the way for the development of new functional food products based on local wisdom, which not only benefit health but also have the potential to improve community well-being through the local food industry (Dahiya & Nigam, 2022; Rahman et al., 2023).

This research is also supported by recent findings on the interaction between gut microbiota and the immune system (Askari et al., 2021; Markowiak & Śliżewska, 2017; Roberfroid, 2007). For instance, research by (Wu et al., 2011) indicates that gut microbiota diversity can influence host immune responses, and synbiotics can play a role in enhancing this diversity. Thus, Dangke synbiotics and dahlia tuber inulin can provide dual benefits: as probiotic and prebiotic sources that support gut microbiota health and as potential immunomodulatory agents.

In a global context, this study contributes to a broader understanding of the benefits of synbiotics and the importance of exploring local resources for developing sustainable health solutions (Hill et al., 2014). Therefore, this research not only has the potential to directly benefit public health but also enriches scientific knowledge on synbiotics and immunomodulation.

RESEARCH METHODS

This study is quantitative research with an experimental approach aimed at observing the effects of administering synbiotics containing Lactic Acid Bacteria (LAB) and inulin extract from dahlia tubers on body weight and immune response in mice. The research design employs a completely randomized design pattern with four treatment groups. Treatment groups include a negative control (P0), and synbiotics administration at doses of 0.25 mL/30gBW (P1), 0.5 mL/30gBW (P2), and 0.75 mL/30gBW (P3). The mice used in this study are male ICR strain mice weighing the independent variables in this study were the synbiotic dose given, while the dependent variables measured included changes in body weight (measured every five days), macrophage phagocytosis activity (measured at day 21), and lymphoid organ index (liver and spleen weight compared to total body weight, measured after euthanasia).

Identification and Inulin Extraction

The dahlia tubers used in this study have been taxonomically identified and confirmed as *Dahlia pinnata* which belongs to the family Asteraceae. The identification was carried out by Dr. Masriany, M.Si, a botanist at the Botanical Laboratory, Department of Biology, Faculty of Science and Technology, UIN Alauddin. The inulin extraction process begins with cleaning, peeling, washing, cutting, and cooking the cut dahlia bulbs. After that, the dahlia tuber pieces are blended and filtered. The resulting filtrate is mixed with absolute ethanol (Merck, Germany, PA grade) in a ratio of 1:3, then left at 4°C overnight and centrifuged using a centrifuge (Thermo Scientific Heraeus™ Multifuge X1R, Germany) at 10,000 rpm for 15 minutes to obtain inulin precipitate. The presence of inulin was confirmed using the Seliwanoff reagent (Sigma-Aldrich, USA).

Synbiotic Preparation

The Lactic Acid (BAL) bacteria used in this study is Lactobacillus fermentum which was isolated from Dangke. This isolate is maintained at the Microbiology Laboratory, Faculty of Agriculture, Hasanuddin University. BAL was reactivated by growing cultures in MRSB (De Man, Rogosa, and Sharpe Broth, Oxoid, UK) and MRSA (Oxoid, UK) media for 24 hours at 37°C. After the culture is obtained, a gradual dilution is carried out to obtain the appropriate concentration. Synbiotic preparation is carried out by mixing fresh cow's milk (Ultra Milk, PT. Ultrajaya, Indonesia) with skimmed milk (Difco™, USA) and inulin extracted from dahlia bulbs. This mixture is then inoculated with BAL culture and incubated at a temperature of 37°C until a pH reaches 5. The incubation process lasts for 24 hours, and the resulting synbiotic is stored in a brown vial bottle (Iwaki, Japan) at 4°C until ready to be given to experimental animals.

Experimental Animals and Treatment Procedures

A total of 28 male mice of the ICR strain with a weight between 25-40 g were obtained from the Animal Experiment Unit, Faculty of Medicine, Hasanuddin University. These mice were acclimatized for 6 days with standard feeding (AD1 Feed, PT. Charoen Pokphand, Indonesia) and drinking water ad libitum. After the acclimatization period, mice were randomly divided into four treatment groups according to the synbiotic dose to be administered: P0 (negative control), P1 (0.25 mL/30g BB), P2 (0.5 mL/30g BB), and P3 (0.75 mL/30g BB). Synbiotic administration was carried out orally every morning using an oral probe (Narishige, Japan) for 20 consecutive days.

Weight Measurement and Immunological Parameters

The mice weight was measured every five days using a digital analytical scale (Mettler Toledo ML204, Switzerland). Macrophage phagocytosis activity was evaluated on day 21 using the carbon method. The mice were given an injection of Indian (Pelican, German) ink suspension through a caudal vein, and blood samples were taken at intervals of 0, 5, and 10 minutes. The absorbance of the blood sample was measured using the UV-Vis spectrophotometer (Shimadzu UV-1800, Japan). After the animal is euthanasian, the spleen and liver organs are removed, then weighed using a pocket scale (Camry EK5055, China) to calculate the organ index, which is expressed as a ratio of organ weight to 100 g of the total body weight of the mice.

All of these research procedures have been approved by the Ethics Committee of the Faculty of Medicine and Health Sciences, Alauddin State Islamic University, Makassar with approval number C.016/KEPK/FKIK/I/2023. All handling and experimental procedures on experimental animals follow applicable guidelines and ethical standards for the use of laboratory animals.

Data Analysis

The data obtained were analyzed using the SPSS program version 25.0 (IBM Corp., Armonk, NY, USA). The statistical test used was one-way variant analysis (One-Way ANOVA) to determine differences between groups, followed by a Duncan follow-up test to see significant differences between treatments at a confidence level of 95% ($p < 0.05$).

RESEARCH RESULT

The first parameter evaluated in this study was the change in body weight of mice during the 20-day synbiotics treatment period. As illustrated in Figure 1, all treatment groups exhibited an upward trend in body weight compared to the initial measurements. The control group (P0), which received no synbiotics, showed the smallest average weight gain. In contrast, the groups receiving synbiotics at doses of 0.25 mL/30g BW (P1) and 0.5 mL/30g BW (P2) experienced more substantial weight increases. The group receiving the highest dose (P3; 0.75 mL/30g BW) also showed an increase, although not as pronounced as P1 and P2. Statistical analysis using one-way ANOVA confirmed a significant difference in weight gain between the groups ($p < 0.05$), particularly between the control and P1 and P2 groups. According to Duncan's multiple range test, P1 and P2 formed a homogenous subset, indicating no significant difference between these two doses, while both were significantly different from the control group.

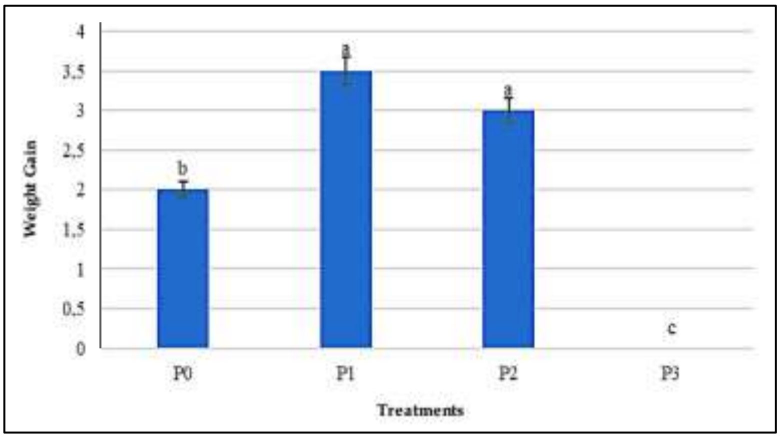

Figure 1. The mean of mice weight gain over the 20-day treatment period. Similar letters indicate no significant difference in Duncan's analysis.

The second parameter measured was the phagocytosis constant, which reflects the macrophage activity in eliminating foreign particles and is a critical indicator of innate immune function. As shown in Figure 2, all groups demonstrated phagocytic activity, but there were clear differences in magnitude.

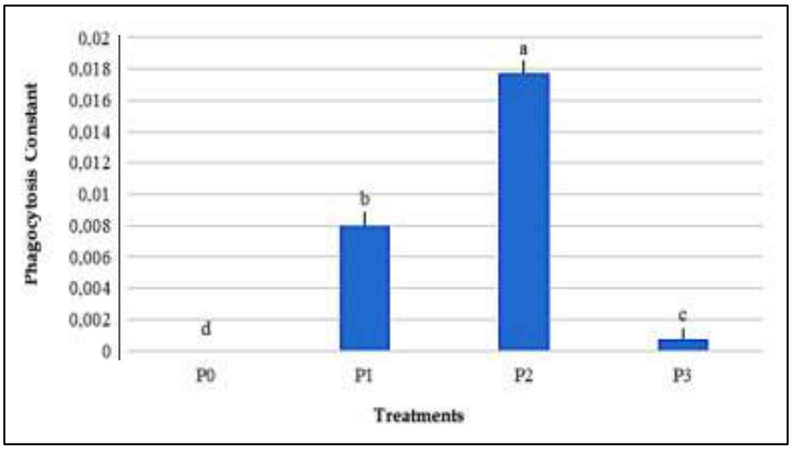

Figure 2. The mean values of macrophage phagocytosis were constant in mice over 20 days of treatment. Similar letters indicate no significant difference in Duncan's analysis.

The control group displayed the lowest mean phagocytosis constant, while the treated groups showed progressive increases corresponding to the dose administered. The P3 group (0.75 mL/30g BW) achieved the highest mean value, suggesting a dose-dependent enhancement of immune function. Statistical analysis revealed that these increases were statistically significant ($p < 0.05$). The results suggest that synbiotics can stimulate the macrophage phagocytic response, thereby improving immune surveillance in mice.

The third parameter assessed in this study was the organ index of the liver and spleen, which serves as an indicator of systemic physiological responses, including inflammation or immune organ hypertrophy. The data presented in Figure 3 show that mice treated with synbiotics exhibited increased organ indices compared to the control group. The spleen index, in particular, was notably higher in the P2 and P3 groups, while the liver index showed moderate elevation across all treated groups.

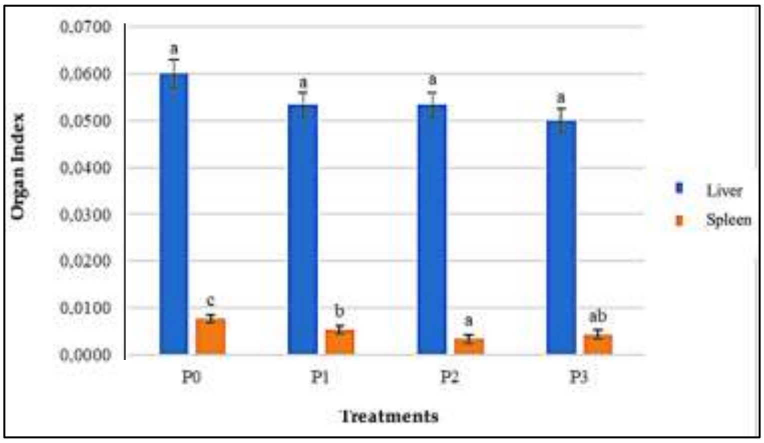

Figure 3. The Liver and spleen organ index of mice during 20 days of treatment. Notations with the same letter show an insignificant difference in Duncan's analysis.

These observations suggest an activation of immune-associated organs in response to synbiotics. One-way ANOVA indicated that the differences between groups were statistically significant ($p < 0.05$), with Duncan's test confirming distinct groupings between the control and higher dose treatments. These findings support the hypothesis that synbiotics contribute to enhancing immune organ function.

DISCUSSION

The observed changes in body weight following synbiotics administration suggest a potential impact of probiotics and prebiotics on metabolism and nutrient absorption. The significant weight gain in groups P1 and P2 compared to the control group indicates that synbiotics may enhance physiological functions related to growth. To understand this effect, several mechanisms can be considered based on previous scientific findings.

The weight gain observed in mice administered with synbiotics can be associated with several mechanisms supported by scientific literature. One possible mechanism is the enhancement of nutrient absorption efficiency in the gut induced by probiotics and prebiotics within the synbiotics (Peng et al., 2019). According to research by (McFarland, 2015), probiotics can improve gut health by stimulating digestive enzyme production and enhancing intestinal mucosal integrity. This study suggests that probiotics can increase nutrient absorption and metabolism, contributing to weight gain.

Furthermore, prebiotics such as the inulin used in this study play a crucial role in supporting beneficial gut microbiota growth (Abdurrahman et al., 2016; Kaewarsar et al., 2023; Kusmiyati et al., 2018). Prebiotics are indigestible by human digestive enzymes but are fermented by gut microorganisms, producing Short-Chain fatty acids (SCFA) that benefit gut health and body metabolism (Slavin, 2013). SCFA production from inulin fermentation helps improve the absorption of minerals like calcium and magnesium, essential for weight growth and maintenance (Devkar et al., 2012; Lauzon et al., 2014; Roberfroid, 2007; Roberfroid et al., 2016; Slavin, 2013).

This study also aligns with findings by (Everard et al., 2013), showing that inulin supplementation can increase *bifidobacteria* populations in the guts of rats, contributing to weight gain and body composition improvement. *Bifidobacteria* can digest non-digestible fibres and produce SCFA, which regulates energy metabolism and reduces gut inflammation (Song et al., 2021).

Apart from effects on nutrient absorption and metabolism, synbiotics also play a role in modulating the immune system, impacting overall growth and health in mice (Srirengaraj et al., 2023; Wan et al., 2019). Probiotics are known to interact with immune cells in the gut, such as macrophages and lymphocytes, and modulate the production of pro- and anti-inflammatory cytokines (Sanders et al., 2013). Studies by (Rodríguez-Nogales et al., 2018; Wang et al., 2019) found that probiotic supplementation can enhance macrophage phagocytic activity and interferon-γ (IFN-γ) production, aiding in more effective immune responses to infection and inflammation, thereby supporting weight gain and maintenance.

However, it is important to consider several other factors that may influence the outcomes of this research. Genetic variability among mice, environmental conditions, and the duration of synbiotics administration could all be factors influencing results (Pena Quintana, L. & Serra

Majem, L., 2000). Therefore, further research with tighter controls and deeper analysis is needed to verify these findings.

The observed increase in the phagocytosis constant following synbiotics treatment suggests that the combination of probiotics and prebiotics contributes to enhancing immune function. The phagocytic activity of macrophages is a key component of innate immunity, serving as the body's first line of defence against pathogens (Silva-Comar et al., 2014). Several underlying mechanisms may explain the immunomodulatory effects observed in this study.

Synbiotics, comprising a combination of probiotics and prebiotics, play a crucial role in modulating the body's immune response (Askari et al., 2021). Probiotics are known to enhance immune function, including macrophage phagocytic activity, which is one of the body's first lines of defence against pathogenic infections (Doron & Snydman, 2015).

Research by (Parvez et al., 2006) demonstrated that probiotic consumption can increase phagocytic activity and the production of pro-inflammatory cytokines such as IL-1β and TNF-α, which play a role in activating and enhancing the phagocytic abilities of immune cells. This increased phagocytic activity aids in the efficient elimination of pathogens and foreign particles (Yamaguchi et al., 2020), as reflected in the increased phagocytosis constant observed in this study.

Additionally, prebiotics like inulin used in this study support the growth of beneficial gut microbiota, which in turn interacts with the immune system through several mechanisms (Roberfroid et al., 2016). Prebiotics are fermented by the gut microbiota into Short-Chain fatty acids (SCFAs) such as butyrate, acetate, and propionate, which have modulatory effects on the immune system (Macfarlane & Macfarlane, 2003). SCFAs can influence macrophage function by increasing the production of anti-inflammatory cytokines and reducing the production of pro-inflammatory cytokines, thereby supporting a healthier immune balance and enhancing phagocytic activity (Vinolo et al., 2011).

A report by (Salvo-Romero et al., 2020) supports these findings, showing that synbiotics supplementation can increase the expression of receptors on macrophages crucial for the process of phagocytosis, such as TLR2 and TLR4. These receptors play a key role in pathogen recognition and the effective activation of immune responses (Salvo-Romero et al., 2020). With increased receptor expression, macrophages become more efficient in recognizing and destroying pathogens, which may explain the observed increase in the phagocytosis constant in this study (Mukherjee et al., 2016).

The improvement in liver and spleen health, indicated by the reduction in organ indices in mice treated with synbiotics, suggests a protective effect against inflammation and oxidative stress. The liver and spleen play crucial roles in metabolism, detoxification, and immune function, making them key indicators of overall physiological health (Dajti et al., 2021; Kurniawan et al., 2020). The observed effects can be explained through several mechanisms supported by scientific literature.

Synbiotics, which combine probiotics and prebiotics, have a synergistic effect in modulating organ health, particularly the liver and spleen (He et al., 2024; Simon et al., 2021). Probiotics have been shown to have hepatoprotective effects by reducing inflammation and oxidative stress in the liver (Jantararussamee et al., 2021; Kusumawati et al., 2022). Studies by (Kirpich et al., 2008) demonstrate that probiotic consumption can mitigate alcohol-induced liver damage by reducing liver enzyme levels and inflammation. Probiotics work by balancing gut microbiota, thereby reducing the production of toxins that can reach the liver through the portal circulation and cause hepatocyte damage (Phumcharoen & Sittiprapaporn, 2021).

Prebiotics like inulin also contribute to liver health by increasing the production of Short-Chain fatty acids (SCFA) such as butyrate, which have anti-inflammatory effects and support liver cell regeneration ((Palatty et al., 2023). SCFA also serve as the energy source for hepatocytes and improves gut barrier function, preventing the translocation of pathogenic bacteria and endotoxins to the liver (Ji et al., 2018).

In addition to their direct effects on the liver, synbiotics also impact spleen health, a vital organ in the immune system and blood filtration (Lewis et al., 2019). The decrease in the spleen index in the synbiotics treatment group indicates a reduction in inflammation and oxidative stress activity (Lan et al., 2020). Probiotics can induce the production of anti-inflammatory cytokines such as IL-10, which reduces systemic inflammation and decreases spleen size often enlarged due to inflammatory responses (Gill et al., 2001).

Furthermore, the combination of probiotics and prebiotics in synbiotics enhances adaptive immune response by increasing the production of immune cells such as lymphocytes and macrophages, and improving phagocytic activity as discussed earlier. This supports spleen health, which functions as a centre for processing red blood cells and regulating the body's immune response (Bronte & Pittet, 2013; Lewis et al., 2019).

This study highlights the potential of synbiotics as functional agents to improve immune function, support organ health, and enhance growth performance. The findings reinforce existing evidence on the positive impact of gut microbiota modulation and may inform future applications in clinical nutrition and preventive health. However, the study's limitations include its short duration, small sample size, and lack of molecular data, such as cytokine expression or gut microbiota analysis, which restrict the understanding of underlying mechanisms. Additionally, individual variability and environmental influences were not fully controlled. Future studies should address these gaps by incorporating longer observation periods, larger cohorts, and integrative molecular analyses to better elucidate the pathways through which synbiotics exert their effects and to enhance their translational relevance.

CONCLUSION

This study demonstrates that administering synbiotics to mice has a positive impact on increasing body weight, enhancing phagocytosis activity, and reducing liver and spleen organ indices. Synbiotics improve metabolic efficiency and nutrient absorption, strengthen the immune system by enhancing phagocytic activity, and provide protective effects on vital organs by reducing inflammation and oxidative stress. These findings highlight the potential of synbiotics as supplements for the prevention and treatment of metabolic, immune-related, and organ health conditions, paving the way for clinical applications of synbiotics to enhance human health.

ACKNOWLEDGMENTS

We sincerely express our gratitude to all parties who have supported this research. We extend our thanks to the Department of Biology, UIN Alauddin, for the facilities provided. Our highest appreciation also goes to the Microbiology Laboratory team for their technical assistance and support throughout the research.

REFERENCE

Abdurrahman, Z. H., Pramono, Y. B., & Suthama, N. (2016). Feeding effect of inulin derived from dahlia tuber combined with Lactobacillus sp. On meat protein mass of crossbred kampong chicken. *Journal of the Indonesian Tropical Animal Agriculture*, *41*(1), 37–44. https://doi.org/10.14710/jitaa.41.1.37-44

Al-Fataftah, S. M., Alshawabkeh, K., & Ibrahim, S. A., & A. R. A., Herzallah. (2013). Administration of lactic acid bacteria to enhance synthesis of vitamin B12 and B6 and lower cholesterol levels in poultry meat. *Journal of Food, Agriculture and Environment*, *11(2)*, 604-609.

Askari, G., Ghavami, A., Shahdadian, F., & Moravejolahkami, A. R. (2021). Effect of synbiotics and probiotics supplementation on autoimmune diseases: A systematic review and metaanalysis of clinical trials. *Clinical Nutrition*, *40*(5), 3221–3234. https://doi.org/10.1016/j.clnu.2021.02.015

Azad, M. A. K., Sarker, M., Li, T., & Yin, J. (2018). Probiotic Species in the Modulation of Gut Microbiota: An Overview. *BioMed Research International*, *2018*(1), 1–8. https://doi.org/10.1155/2018/9478630

Balta, I., Butucel, E., Mohylyuk, V., Criste, A., Dezmirean, D. S., Stef, L., Pet, I., & Corcionivoschi, N. (2021). Novel Insights into the Role of Probiotics in Respiratory Infections, Allergies, Cancer, and Neurological Abnormalities. *Diseases*, *9*(3), 60. https://doi.org/10.3390/diseases9030060

Bronte, V., & Pittet, M. J. (2013). The Spleen in Local and Systemic Regulation of Immunity. *Immunity*, *39*(5), 806–818. https://doi.org/10.1016/j.immuni.2013.10.010

Burhan, H., Priyambada, S. A., Taufik, E., & Arief, I. I. (2017). Potential of lactic acid bacteria isolated from Dangke and Indonesian beef as hypocholesterolaemic agent. *Media Peternakan*, *40*(2), 136–142. https://doi.org/10.5398/medpet.2017.40.2.136

Dahiya, D., & Nigam, P. S. (2022). Probiotics, Prebiotics, Synbiotics, and Fermented Foods as Potential Biotics in Nutrition Improving Health via Microbiome-Gut-Brain Axis. *Fermentation*, *8*(7), 303. https://doi.org/10.3390/fermentation8070303

Dajti, E., Marasco, G., Ravaioli, F., Alemanni, L. V., Rossini, B., Colecchia, L., Vestito, A., Festi, D., & Colecchia, A. (2021). The role of liver and spleen elastography in advanced chronic liver disease. *Minerva Gastroenterology*, *67*(2). https://doi.org/10.23736/S2724-5985.20.02793-2

Devkar, N., Chauhan, V., & Vibhute, A. (2012). Probiotics and Prebiotics in Periodontal Disease-Revisited. *Journal of Dental and Allied Sciences*, *1*(1), 18. https://doi.org/10.4103/2277-4696.159110

Djide, N. J. N., Yanti, N. I., Pratiwi, N. S., Nuzulia, A. A., & Asri, R. M. (2021). Assessment of probiotic properties and safety of lactic acid bacteria isolated from South Sulawesi ethnic cheese. *Journal of Experimental Biology and Agricultural Sciences*, *9*(Spl-2-ICOPMES_2020), S222–S227. https://doi.org/10.18006/2021.9(Spl-2-ICOPMES_2020).S222.S227

Doron, S., & Snydman, D. R. (2015). Risk and safety of probiotics. *Clinical Infectious Diseases*, *60*(1), S129–S134. https://doi.org/10.1093/cid/civ085

Everard, A., Belzer, C., Geurts, L., Ouwerkerk, J. P., Druart, C., Bindels, L. B., Guiot, Y., Derrien, M., Muccioli, G. G., Delzenne, N. M., De Vos, W. M., & Cani, P. D. (2013). Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(22), 9066–9071. https://doi.org/10.1073/pnas.1219451110

Gill, H. S., Rutherfurd, K. J., Cross, M. L., & Gopal, P. K. (2001). Enhancement of immunity in the elderly by dietary supplementation with the probiotic Bifidobactedum lactis HN019. *American Journal of Clinical Nutrition*, *74*(6), 833–839. https://doi.org/10.1093/ajcn/74.6.833

Goyal, S., Sharma, K., & Ajeet, A. (2015). Probiotic and prebiotic: Current status and their future perspectives. *World Journal of Pharmacy and Pharmaceutical Sciences*, *4*(10), 234–256.

He, F., Ma, X.-K., Tu, C.-K., Teng, H., Shao, X., Chen, J., & Hu, M.-X. (2024). Lactobacillus reuteri biofilms formed on porous zein/cellulose scaffolds: Synbiotics to regulate intestinal microbiota. *International Journal of Biological Macromolecules*, *262*, 130152. https://doi.org/10.1016/j.ijbiomac.2024.130152

Hill, C., Guarner, F., Reid, G., Gibson, G. R., Merenstein, D. J., Pot, B., Morelli, L., Canani, R. B., Flint, H. J., Salminen, S., Calder, P. C., & Sanders, M. E. (2014). Expert consensus document: The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology and Hepatology*, *11*(8), 506–514. https://doi.org/10.1038/nrgastro.2014.66

Hutkins, R. W., Krumbeck, J. A., Bindels, L. B., Cani, P. D., Fahey, G., Goh, Y. J., Hamaker, B., Martens, E. C., Mills, D. A., Rastal, R. A., Vaughan, E., & Sanders, M. E. (2016). Prebiotics: Why definitions matter. In *Current Opinion in Biotechnology* (Vol. 37, pp. 1–7). https://doi.org/10.1016/j.copbio.2015.09.001

Jantararussamee, C., Rodniem, S., Taweechotipatr, M., Showpittapornchai, U., & Pradidarcheep, W. (2021). Hepatoprotective Effect of Probiotic Lactic Acid Bacteria on Thioacetamide-Induced Liver Fibrosis in Rats. *Probiotics and Antimicrobial Proteins*, *13*(1), 40–50. https://doi.org/10.1007/s12602-020-09663-6

Ji, X., Zhou, F., Zhang, Y., Deng, R., Xu, W., Bai, M., Liu, Y., Shao, L., Wang, X., & Zhou, L. (2018). Butyrate stimulates hepatic gluconeogenesis in mouse primary hepatocytes. *Experimental and Therapeutic Medicine*. https://doi.org/10.3892/etm.2018.7136

Kaewarsar, E., Chaiyasut, C., Lailerd, N., Makhamrueang, N., Peerajan, S., & Sirilun, S. (2023). Effects of Synbiotic Lacticaseibacillus paracasei, Bifidobacterium breve, and Prebiotics on the Growth Stimulation of Beneficial Gut Microbiota. *Foods*, *12*(20), 3847. https://doi.org/10.3390/foods12203847

Kechagia, M., Basoulis, D., Konstantopoulou, S., Dimitriadi, D., Gyftopoulou, K., Skarmoutsou, N., & Fakiri, E. M. (2013). Health Benefits of Probiotics: A Review. *ISRN Nutrition*, *2013*(1), 1–7. https://doi.org/10.5402/2013/481651

Kirpich, I. A., Solovieva, N. V., Leikhter, S. N., Shidakova, N. A., Lebedeva, O. V., Sidorov, P. I., Bazhukova, T. A., Soloviev, A. G., Barve, S. S., McClain, C. J., & Cave, M. (2008). Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: A pilot study. *Alcohol*, *42*(8), 675–682. https://doi.org/10.1016/j.alcohol.2008.08.006

Kurniawan, D. W., Storm, G., Prakash, J., & Bansal, R. (2020). Role of spleen tyrosine kinase in liver diseases. *World Journal of Gastroenterology*, *26*(10), 1005–1019. https://doi.org/10.3748/wjg.v26.i10.1005

Kusmiyati, N., Wahyunings, T. D., & . W. (2018). Prebiotic Effect of Inulin Extract from Dahlia Tubers (Dahlia Pinnata L.) On the Growth Performance of Intestinal-origin Lactobacillus Casei AP. *Pakistan Journal of Nutrition*, *17*(8), 405–410. https://doi.org/10.3923/pjn.2018.405.410

Kusumawati, N. R., Ulfah, M. M., Panunggal, D. G., Sudarmo, S. M., Utari, M. A., & Sidhartani, M. (2022). Hepatoprotective Effects of Probiotic Administration on High Fat-High Fructose Diet Induced Nonalcoholic Steatohepatitis in Sprague-Dawley Rats. *International Journal of Probiotics and Prebiotics*, *18*(1), 1–6. https://doi.org/10.37290/ijpp2641-7197.18:1-6

Lan, R., Wei, L., Chang, Q., Wu, S., & Zhihui, Z. (2020). Effects of dietary chitosan oligosaccharides on oxidative stress and inflammation response in liver and spleen of yellow-feather broilers exposed to high ambient temperature. *Italian Journal of Animal Science*, *19*(1), 1508–1517. https://doi.org/10.1080/1828051X.2020.1850215

Lauzon, H. L., Dimitroglou, A., Merrifield, D. L., Ringø, E., & Davies, S. J. (2014). Probiotics and prebiotics: Concepts, definitions and history. In *Aquaculture Nutrition: Gut Health, Probiotics and Prebiotics* (pp. 169–184). https://doi.org/10.1002/9781118897263.ch7

Lewis, S. M., Williams, A., & Eisenbarth, S. C. (2019). Structure and function of the immune system in the spleen. *Science Immunology*, *4*(33), eaau6085. https://doi.org/10.1126/sciimmunol.aau6085

Macfarlane, S., & Macfarlane, G. T. (2003). Regulation of short-chain fatty acid production. *Proceedings of the Nutrition Society*, *62*(1), 67–72. https://doi.org/10.1079/pns2002207

Markowiak, P., & Śliżewska, K. (2017). Effects of Probiotics, Prebiotics, and Synbiotics on Human Health. *Nutrients*, *9*(9), 1021. https://doi.org/10.3390/nu9091021

McFarland, L. V. (2015). From yaks to yogurt: The history, development, and current use of probiotics. *Clinical Infectious Diseases*, *60*(1), S85–S90. https://doi.org/10.1093/cid/civ054

Mukherjee, S., Karmakar, S., & Babu, S. P. S. (2016). TLR2 and TLR4 mediated host immune responses in major infectious diseases: A review. *The Brazilian Journal of Infectious Diseases*, *20*(2), 193–204. https://doi.org/10.1016/j.bjid.2015.10.011

Mustamin, S. F., Jumadi, & Sumilih, D. A. (2022). *Dangke: Pangan Lokal (Kajian Historis dan Nilai Budaya di Desa Pinang Kecamatan Cendana Kabupaten Enrekang)*. *6*(1), 74.

Nur, F. (2012). Isolation of Lactic Acid Bacteria As a Potential Probiotic in Dangke , a Traditional Food From Buffalo Milk. *International Journal of Sciences: Basic and Applied Research (IJSBAR)*, *35*(1).

Palatty, P. L., Jakribettu, R. P., Sacheendran, D., Varghese, N. K., Yashawant, H. S., Raghu, S. V., Prabhakar, P., Pavankumar, G. S., & Baliga, M. S. (2023). Role of Probiotics and Synbiotics in Mitigating Alcohol-Induced Liver Damage. In *Synbiotics for the Management of Cancer* (pp. 315–328). https://doi.org/10.1007/978-981-19-7550-9_16

Parvez, S., Malik, K. A., Ah Kang, S., & Kim, H. Y. (2006). Probiotics and their fermented food products are beneficial for health. In *Journal of Applied Microbiology* (Vol. 100, Issue 6, pp. 1171–1185). https://doi.org/10.1111/j.1365-2672.2006.02963.x

Pena Quintana, L., & Serra Majem, L. (2000). Use of probiotics, prebiotics and synbiotics in human patology: Preventive and threpuetics efects. *Pediatrika*, *20*(8), 9–19.

Peng, M., Patel, P., Nagarajan, V., Bernhardt, C., Carrion, M., & Biswas, D. (2019). Feasible Options to Control Colonization of Enteric Pathogens With Designed Synbiotics. In *Dietary Interventions in Gastrointestinal Diseases* (pp. 135–149). Elsevier. https://doi.org/10.1016/B978-0-12-814468-8.00011-9

Phumcharoen, P., & Sittiprapaporn, W. (2021). Investigation of Synbiotic Effect in Thai Night Shift Workers Identified by Epworth Sleepiness Scales. *International Journal on Advanced Science,* *Engineering and Information Technology*, *11*(5), 2002. https://doi.org/10.18517/ijaseit.11.5.16000

Rahman, S., Lasumange, & Yunus, A. (2023). Historical overview and contribution of Dangke as traditional food to incomeand public health. *Food Research*, *7*(5), 245–250. https://doi.org/10.26656/fr.2017.7(5).964

Roberfroid, M. (2007). Effects of Probiotics and Prebiotics Prebiotics: The Concept Revisited. *The Journal of Nutrition*, *137*(3).

Roberfroid, M., Gibson, G. R., Hoyles, L., McCartney, A. L., Rastall, R., Rowland, I., Wolvers, D., Watzl, B., Szajewska, H., Stahl, B., Guarner, F., Respondek, F., Whelan, K., Coxam, V., Davicco, M.-J., Léotoing, L., Wittrant, Y., Delzenne, N. M., Cani, P. D., … Meheust, A. (2016). Prebiotic concept and health. *British Journal of Nutrition*, *104*(S2), S1–S63.

Rodríguez-Nogales, A., Algieri, F., Garrido-Mesa, J., Vezza, T., Utrilla, M. P., Chueca, N., García, F., Rodríguez-Cabezas, M. E., & Gálvez, J. (2018). Intestinal anti-inflammatory effect of the probiotic Saccharomyces boulardii in DSS-induced colitis in mice: Impact on microRNAs expression and gut microbiota composition. *Journal of Nutritional Biochemistry*, *61*(1), 129–139. https://doi.org/10.1016/j.jnutbio.2018.08.005

Saad, N., Delattre, C., Urdaci, M., Schmitter, J. M., & Bressollier, P. (2013). An overview of the last advances in probiotic and prebiotic field. In *LWT* (Vol. 50, Issue 1, pp. 1–16). https://doi.org/10.1016/j.lwt.2012.05.014

Salvo-Romero, E., Stokes, P., & Gareau, M. G. (2020). Microbiota-immune interactions: From gut to brain. *LymphoSign Journal*, *7*(1), 1–23. https://doi.org/10.14785/lymphosign-2019-0018

Sanders, M. E., Guarner, F., Guerrant, R., Holt, P. R., Quigley, E. M. M., Sartor, R. B., Sherman, P. M., & Mayer, E. A. (2013). An update on the use and investigation of probiotics in health and disease. *Gut*, *62*(5), 787–796. https://doi.org/10.1136/gutjnl-2012-302504

Silva-Comar, F. M. D. S., Wiirzler, L. A. M., Silva-Filho, S. E., Kummer, R., Pedroso, R. B., Spironello, R. A., Silva, E. L., Bersani-Amado, C. A., & Cuman, R. K. N. (2014). Effect of Estragole on Leukocyte Behavior and Phagocytic Activity of Macrophages. *Evidence-Based Complementary and Alternative Medicine*, *2014*(1), 784689. https://doi.org/10.1155/2014/784689

Simon, E., Călinoiu, L. F., Mitrea, L., & Vodnar, D. C. (2021). Probiotics, Prebiotics, and Synbiotics: Implications and Beneficial Effects against Irritable Bowel Syndrome. *Nutrients*, *13*(6), 2112. https://doi.org/10.3390/nu13062112

Slavin, J. (2013). Fiber and prebiotics: Mechanisms and health benefits. In *Nutrients* (Vol. 5, Issue 4, pp. 1417–1435). https://doi.org/10.3390/nu5041417

Song, Q., Wang, Y., Huang, L., Shen, M., Yu, Y., Yu, Q., Chen, Y., & Xie, J. (2021). Review of the relationships among polysaccharides, gut microbiota, and human health. *Food Research International*, *140*, 109858. https://doi.org/10.1016/j.foodres.2020.109858

Srirengaraj, V., Razafindralambo, H. L., Rabetafika, H. N., Nguyen, H.-T., & Sun, Y.-Z. (2023). Synbiotic Agents and Their Active Components for Sustainable Aquaculture: Concepts, Action Mechanisms, and Applications. *Biology*, *12*(12), 1498. https://doi.org/10.3390/biology12121498

Vinolo, M. A. R., Rodrigues, H. G., Nachbar, R. T., & Curi, R. (2011). Regulation of inflammation by short chain fatty acids. In *Nutrients* (Vol. 3, Issue 10, pp. 858–876). https://doi.org/10.3390/nu3100858

Wan, M. L. Y., Ling, K. H., El-Nezami, H., & Wang, M. F. (2019). Influence of functional food components on gut health. *Critical Reviews in Food Science and Nutrition*, *59*(12), 1927–1936. https://doi.org/10.1080/10408398.2018.1433629

Wang, W., Xing, W., Wei, S., Gao, Q., Wei, X., Shi, L., Kong, Y., & Su, Z. (2019). Semi-rational screening of probiotics from the fecal flora of healthy adults against DSS-induced colitis mice by enhancing anti-inflammatory activity and modulating the gut microbiota. *Journal of Microbiology and Biotechnology*, *29*(9). https://doi.org/10.4014/jmb.1807.06061

Wu, G. D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y. Y., Keilbaugh, S. A., Bewtra, M., Knights, D., Walters, W. A., Knight, R., Sinha, R., Gilroy, E., Gupta, K., Baldassano, R., Nessel, L., Li, H., Bushman, F. D., & Lewis, J. D. (2011). Linking long-term dietary patterns with gut microbial enterotypes. *Science*, *334*(6052), 105–108. https://doi.org/10.1126/science.1208344

Yadav, M. K., Kumari, I., Singh, B., Sharma, K. K., & Tiwari, S. K. (2022). Probiotics, prebiotics and synbiotics: Safe options for next-generation therapeutics. *Applied Microbiology and Biotechnology*, *106*(2), 505–521. https://doi.org/10.1007/s00253-021-11646-8

Yamaguchi, Y., Kaida, K., Suenaga, Y., Ishigami, A., Kobayashi, Y., & Nagata, K. (2020). Age-related dysfunction of p53-regulated phagocytic activity in macrophages. *Biochemical and Biophysical Research Communications*, *529*(2), 462–466. https://doi.org/10.1016/j.bbrc.2020.05.121