Pharmacogn J. 2024; 16(1): 181-185
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Research Article

Effect of *Lactiplantibacillus plantarum* IS-10506 on Accelerating Repair of Ketorolac-Induced Gastric Ulcers in Wistar Rats

Mia Ratwita Andarsini[1,2], Andy Darma[1,2], Alpha Fardah Athiyyah[1,2], Khadijah Rizky Sumitro[1,2], Reza Gunadi Ranuh[1,2,*], Fauziah Pratiwi[1,2], Wibi Riawan[3], Widjiati Widjiati[4], Ingrid S Surono[5], and Subijanto Marto Sudarmo[1,2]

ABSTRACT

A gastric ulcer arises due to an imbalance between the stomach's aggressive and defensive factors, one of which can be induced by ketorolac. The gastric mucosa serves as a protective layer against gastric damage. Probiotics may enhance mucosal secretion, reinforcing their barrier function. This study evaluated the effect of *Lactiplantibacillus plantarum* IS-10506 on repairing gastric mucosal injury expressed by Mucin 5AC (MUC5AC) induction from ketorolac in rodent model. In the experiment, 48 male Wistar rats were randomly assigned and segregated into four groups: the control group (K1), the group with ketorolac administration (K2), the group given *L. plantarum* IS-10506 after ketorolac administration (K3), and the group given *L. plantarum* IS-10506 before and after ketorolac administration (K4). Gastric tissue was examined for cells producing MUC5AC via immunohistochemistry. MUC5AC differences between groups were compared using Kruskal–Wallis and Mann–Whitney U tests. Significant differences were observed between each group on Days 5, 7, and 10 of necropsy (p=0.043; p=0.030; p=0.022). The ketorolac group (K2) consistently exhibited the lowest values during all examination days. Group K4 manifested a higher expression of MUC5AC relative to group K3. However, group K3 demonstrated a significantly increased from Day 1 to 10 of necropsy (p=0.030). Administering probiotic *L. plantarum* IS-10506 prior to ketorolac proved beneficial by significantly accelerate (p=0.030) the MUC5AC expression cells and gene expression.

Mia Ratwita Andarsini[1,2], Andy Darma[1,2], Alpha Fardah Athiyyah[1,2], Khadijah Rizky Sumitro[1,2], Reza Gunadi Ranuh[1,2,*], Fauziah Pratiwi[1,2], Wibi Riawan[3], Widjiati Widjiati[4], Ingrid S Surono[5], and Subijanto Marto Sudarmo[1,2]

[1]Department of Child Health, Faculty of Medicine, Universitas Airlangga, Surabaya, INDONESIA.

[2]Department of Child Health, Dr. Soetomo General Academic Hospital, Surabaya, INDONESIA.

[3]Department of Biomolecular Biochemistry, Faculty of Medicine, Brawijaya University, Malang, INDONESIA.

[4]Department of Veterinary Medicine, Faculty of Veterinary Medicine, Airlangga University, East Java, Surabaya, INDONESIA.

[5]Food Technology Department, Faculty of Engineering, Bina Nusantara University, Jakarta, INDONESIA.

Correspondence

Reza Gunadi Ranuh

Child Health, Dr. Soetomo General Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, INDONESIA.

E-mail: gusti.made.reza@fk.unair.ac.id

History

- Submission Date: 16-12-2023;
- Review completed: 16-01-2024.
- Accepted Date: 16-01-2024.

DOI : 10.5530/pj.2024.16.25

Article Available online

http://www.phcogj.com/v16/i1

INTRODUCTION

The gastric mucosal ulcer occurs when aggressive factors overpower the gastric protection mechanisms, leading to necrosis of the mucosal tissue and ultimately resulted in a gastric ulcer [1,2]. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is considered as one of the primary risk factors for gastric ulcers [3]. Ketorolac belongs to a potent class of NSAIDs widely used for postoperative pain treatment and cancer. Several studies have demonstrated that ketorolac has a more pronounced analgesic effect, yet it is five times more gastrotoxic than other NSAIDs [4,5]. The administration of ketorolac increased the relative risk for peptic ulcers by 11.5, making it the highest risk among NSAIDs [3].

When a gastric ulcer develops, various mechanisms are essential for healing, including repair of the gastric mucosa. The gastric mucosa features a two-layer mucus membrane, which serves primarily as the primary protective barrier against ulcer [6]. This mucus is predominantly secreted by surface mucus cells as mucins, which are glycosylated proteins that constitute the gel layer of the stomach's mucus membrane. The production of gastric mucins comes from the encoding of mucin monomers by mucin production-associated genes [7]. The MUCIN5AC (MUC5AC) gene, expressed by the superficial epithelium, forms both the inner, attached mucus layer and the outer, unattached, loose mucus layer [8].

Administering probiotics, which offer health benefits to the gastrointestinal tract, has been explored and developed as an alternative therapy for gastric ulcers [9]. Probiotics confer immunological advantages through mechanisms such as local macrophage activation, changes in the pro/anti-inflammatory cytokine profile, and modulation of responses to antigens. One study found that probiotics reported to stimulated MUC gene expression in intestinal cells, further inhibiting pathogen adhesion and ensuring the protection of intestinal mucosa [10]. Several species of *Lactobacillus* can enhance mucin expression in human intestinal cells [11,12]. Extensive research involving *Lactiplantibacillus plantarum* IS-10506 (before known as *Lactobacillus plantarum* IS-10506 of dadih, an original native probiotic from Indonesia) has been proven as a potential probiotic [13–16]. The *L. plantarum* IS-10506 shown both protective and therapeutic effects on ulcer to the ileal mucosa, so that probiotics potentially play a regenerative role in gastric ulcer repair. This research aimed to study the effect of probiotic on gastric mucosal ulcer induced by ketorolac exposure using *L. plantarum* IS-10506.

MATERIALS AND METHODS

Animals

Forty-eight of 12 weeks male Wistar rats weighing 150–200 grams from the Integrated Research and Testing Laboratory, Universitas Gadjah Mada, were used in this study. Rats were acclimatized for seven days before the procedure and housed in a standard cage (40 cm x 50 cm x 15 cm), with each cage containing four rats, each marked according to the treatment group. Each Wistar rat received food ad libitum according to standard rat diets. Ethical clearance was obtained from the Animal Care and Use Committee, Veterinary Faculty, Universitas Airlangga No. 2.KE.025.03.2021.

Cite this article: Andarsini MR, Darma A, Athiyyah AF, Sumitro KR, Ranuh RG, Pratiwi F, Riawan W, et al. Effect of *Lactiplantibacillus plantarum* IS-10506 on Accelerating Repair of Ketorolac-Induced Gastric Ulcers in Wistar Rats. Pharmacogn J. 2024;16(1): 181-185.

There were four treatment groups: the control group (K1) received distilled water, group with ketorolac administration at 30 mg/kg BW for five days (K2), the group given *L. plantarum* IS-10506 at 1×10^9 CFU/day for seven days after ketorolac administration (K3), and the group *given L. plantarum* IS-10506 for seven days before and after ketorolac administration (K4). All groups were randomly divided to be sacrificed on Days 1, 5, 7, and 10 after ketorolac administration (Figure 1).

Ketorolac

Ketorolac was administered as a suspension in distilled water for five days via a gastric tube (Ketorolac Trometamol, No Reg: DKL 0604425417A1, Dankos Farma, Indonesia), at a dose of 30 mg/kg BW, and the rats were fasted for 6–8 hours prior to administration.

Probiotic

Microencapsulated *L. plantarum* IS-10506 (Gene Bank accession no. DQ 860148) dissolved in 1.5 ml of distilled water, at a dose of 1×10^9 CFU/day. The probiotic was given to the K3 group for seven days after ketorolac administration and to the K4 group for seven days before and continuing for seven days after ketorolac administration.

Corpus tissue collection

The rats underwent necropsy, after which gastric tissue was extracted. The pathologist cleaned the corpus tissue. The preparation process entailed histological and immunohistochemical analyses using cells expressing MUC5AC. The gastric mucosa from the sample was sectioned to a depth of 4 µm and embedded in paraffin. Gastric ulcers were stained with hematoxylin–eosin (HE) for microscopic examination. The cellular expression of MUC5AC (45M1, Thermo Fisher Scientific, Massachusetts, USA) was quantitatively analyzed using immunohistochemistry (IHC) on the corpus tissue, enumerating the number of MUC5AC cells from the average of 20 random fields at 1000x magnification. An independent examiner observed and counted the histological samples with a Nikon E100 microscope (CX21: Olympus, Tokyo, Japan) equipped with a 12-megapixel digital camera, Optilab Advance Plus, and image processing software in the Biomolecular Biochemistry Laboratory, Department of Biomolecular Biochemistry, Faculty of Medicine, Universitas Brawijaya, Indonesia.

Histology

In this study, the primary unit of analysis was the corpus of Wistar rats. The gastric mucosa was examined using HE staining and IHC. MUC5AC expression was identified using IHC staining to observe gastric ulcer repair.

Statistical Analysis

We compared MUC5AC expression both within and between groups to study the effects in each exposure group. The rank-based Kruskal–Wallis test was employed to determine whether there was a statistically significant difference across all groups. Meanwhile, the Mann–Whitney U test was used to identify any significant difference between the medians of the two independent groups. All statistical analyses were executed using SPSS version 26.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Table 1 represent the results of MUC5AC expression of all groups in this study. Significant findings were observed at several points throughout the study. Notably, on Day 5, Group K4 demonstrated a significantly higher expression of MUC5AC (p=0.043) compared to the other groups. This trend continued on Day 7 and Day 10, where Group K4 maintained a higher MUC5AC expression (p=0.030 and p=0.022, respectively) (Table 1). These results suggest that administering *L. plantarum* IS-10506 both before and after the administration ketorolac is effective in preventing the reduction of MUC5AC expression and accelerating the gene's expression.

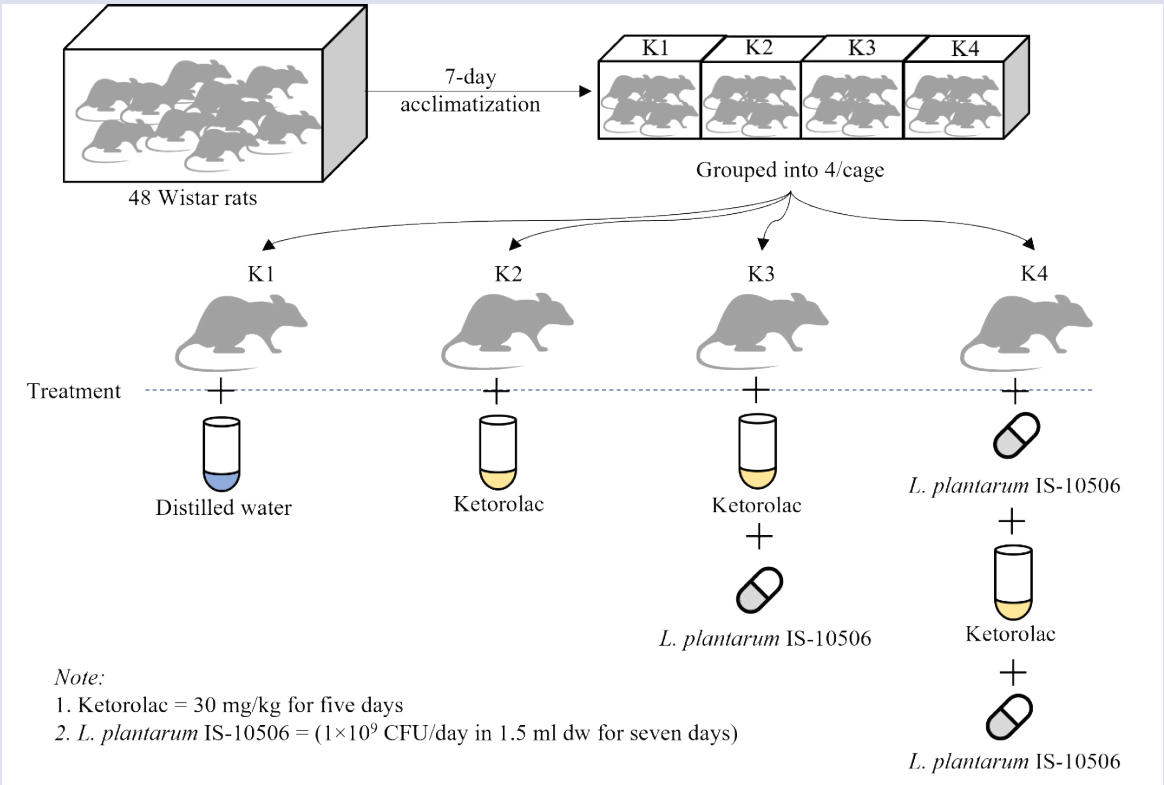

Figure 1. A step-by-step depiction of the procedures for animal preparation and subsequent treatment across different experimental groups.

Table 1. Repair of gastric ulcers from MUC5AC expression.

	Day 1 (Mean ± SD)	Day 5 (Mean ± SD)	Day 7 (Mean ± SD)	Day 10 (Mean ± SD)	p-value
K1	5.3 ± 1.16^{cd}	3.7 ± 0.58^{bc}	3.3 ± 1.16^{abc}	3.7 ± 1.16^{bcd}	0.242
K2	3.0 ± 1.73^{abcd}	2.3 ± 0.58^{ab}	2.3 ± 0.58^{ab}	1.3 ± 0.58^{a}	0.189
K3	3.0 ± 1.00^{abc}	3.7 ± 1.53^{bc}	6.3 ± 0.58^{de}	7.7 ± 1.53^{e}	0.030^{*}
K4	5.3 ± 1.53^{cde}	6.3 ± 0.58^{de}	7.0 ± 1.73^{de}	8.0 ± 1.73^{e}	0.259
p	0.133	0.043^{*}	0.030^{*}	0.022^{*}	

*Indicates significant difference with $p < 0.05$
The same superscript indicates no significant differences.

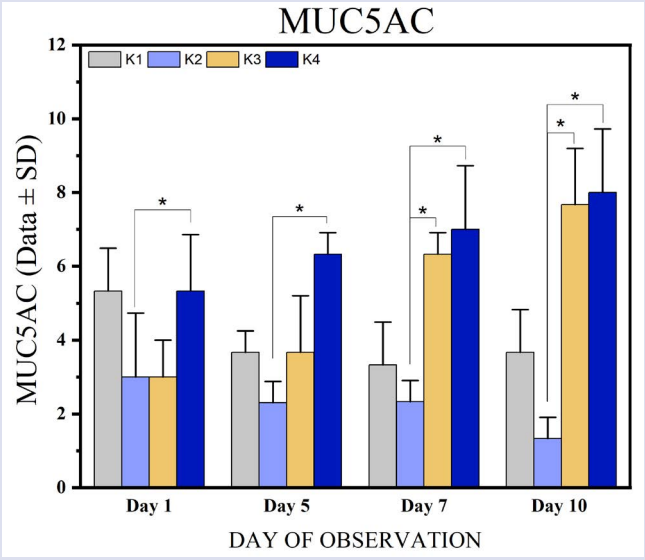

Figure 2. Number of cells expressing MUC5AC during gastric ulcer repair (Mean ± SD, n=48, *$p < 0.05$ for K2 *vs* K3 and K4).

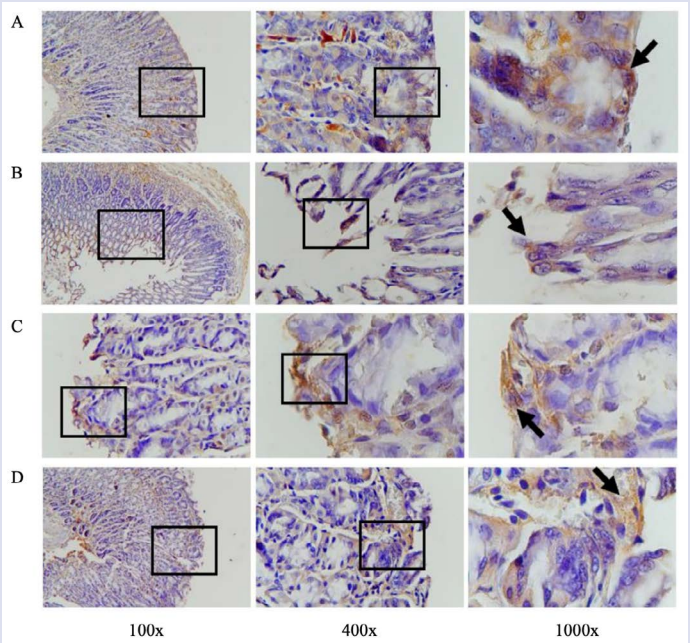

Figure 3. Comparative visualization of MUC5AC expression after ketorolac induction on Day 10 across different groups. Magnifications: Left—100x, Center—400x, and Right—1000x. A) In the control group, MUC5AC expression was analyzed on Day 10. MUC5AC cells, identified by their brownish coloration through IHC staining, are indicated by black arrows. B) For the K2 group, MUC5AC expression was assessed on Day 10 post-necropsy. MUC5AC cells, characterized by their brownish coloration via IHC staining, are highlighted with black arrows. C) In the K3 group, MUC5AC expression was observed on Day 10 post-necropsy. Cells expressing MUC5AC, discernible by their brownish coloration following IHC staining, are marked with black arrows. D) Within the K4 group, MUC5AC expression was examined on Day 10 post-necropsy. The MUC5AC cells, which exhibited a brownish appearance due to IHC staining, are indicated with black arrows.

Additionally, Group K3 showed a substantial increase in MUC5AC expression from Day 1 to Day 10 (p=0.030), indicating that even post-injury administration of the probiotic could aid in the repair process. In contrast, Group K2 consistently showed the lowest MUC5AC expression levels across all days, underscoring the damaging effect of ketorolac on gastric mucosa without probiotic intervention. The administration of *L. plantarum* IS-10506, particularly prior to ketorolac exposure, significantly enhanced the repair of ketorolac-induced gastric ulcers as evidenced by the expression of MUC5AC in the gastric tissue of Wistar rats.

Figure 2 revealed that groups K3 and K4 exhibited a higher number of MUC5AC-expressing cells compared to the control group and Group K2 on Days 5, 7, and 10 (p = 0.043, 0.030, and 0.022, respectively). While starting at the same level as the control group on Day 1, Group K4 showed a consistent increase, peaking at 8.0 ± 1.73 by the end. The figure also demonstrated that Group K3's levels rose steadily, with a marked increase observed between Days 5 and 7. In contrast, the control group saw a moderate decline in levels. The ketorolac group (K2) maintained the lowest values across all examination days. The histopathology of MUC5AC expression is depicted in Figure 3.

DISCUSSIONS

In this study, we evaluated the impact of the probiotic *L. plantarum* IS-10506 on the acceleration of gastric ulcer repair, specifically through the expression of MUC5AC. We observed a decrease in the number of cells expressing MUC5AC on the first day following ketorolac exposure (groups K2 and K3), with the lowest count evident in the ketorolac-only group (K2). Consistent with this, the severity of the gastric mucosal ulcer, as indicated by the histological activity index (HAI), was highest in the ketorolac group [17].

Ketorolac, when administered at a dose of 30 mg/kg BW, has been shown to significantly inhibit the activity of cyclooxygenase (COX) enzymes by up to 91% [18]. The suppression of both COX-1 and COX-2 results in diminished secretion of prostaglandins (PGs). Since PGs play a cytoprotective role in gastric mucosa, their reduced levels lead to increased vulnerability to mucosal ulcer [19]. It is crucial to note that PGs function as potent vasodilators, enhancing mucosal circulation. This increase in circulation aids in neutralizing back-diffusing acid and diluting any toxic agents that might penetrate the subepithelial space. Maintaining this mucosal blood flow is critical to ensure prompt repair of the injured epithelium, preventing further damage to the mucosa [20].

The regeneration period for gastric epithelial cells varies significantly, from 3 to 5 days for surface mucus cells (SMCs) to several months for zymogenic cells [21]. Repair through cell migration for superficial lesions begins within minutes, and regeneration through the proliferation and differentiation of progenitor cells spans days to months [22]. A study on mucosa healing after ketorolac-induced gastric ulcer found that the healing mechanism, when assessed via fibroblast cells, was minimal after 10 days of examination [17]. Our research also indicated that the expression of MUC5AC cells did not increase until Day 10 of examination in the ketorolac group, resulting in a more extended healing process for the gastric mucosa. Normally, gastric mucosa expresses specific cell types, such as MUC1, MUC5AC, and MUC6 [23–25].

SMCs express MUC1 and MUC5AC in the superficial epithelium and upper part of the gastric pits. Meanwhile, MUC6 is expressed in the deep glands. Research on ethanol-induced gastric ulcer in rats demonstrated that the protection mechanism against such damage bolstered MUC5AC and MUC6 levels rather than MUC1 [26]. On the other hand, there was a significant increase in the expression of MUC5AC in cells in the group that received probiotic therapy. Under inflammatory conditions, the oral administration of probiotics helps normalize abnormal mucus secretion and positively affects MUC gene expression in animal models [27–29]. *Lactobacillus rhamnosus GG*, one of the most widely used probiotics, has been reported to increase COX-2 expression and prostaglandin E2 secretion in colonic hemostasis [30]. Prostaglandins are vital mediators that protect the gastrointestinal mucosa and maintain mucosal epithelial barrier integrity [31].

Another benefit of probiotics for gastric mucosa is their ability to upregulate the MUC1 and MUC5AC genes. Probiotics from the *E. coli Nissle 1917* (EcN) strain have been shown to stimulate MUC gene expression in intestinal cells, thereby antagonizing pathogen adhesion and protecting intestinal mucosa [10]. Separate research using a different probiotic strain, *Bifidobacterium BF-1*, found an increase in MUC5AC gene expression and mucus production in SMCs in mice with acute gastric lesions induced by acid or ethanol [7]. Probiotics can also upregulate tight junction proteins and promote mucus secretion by increasing the expression of MUC1, MUC2, and MUC3, thus stabilizing the mucosal surface [32,33].

Research conducted by Dharmani et al. (2013) indicated that the administration of probiotics could promote MUC5AC expression more rapidly in the treatment group than in the control group. Similarly, our study revealed that the two probiotic-intervention groups exhibited a higher number of MUC5AC expression cells compared to the control group. A study with *Lactobacillus gasseri* OLL2716 yogurt showed a significant acceleration of chronic gastric ulcer healing within 10 days [34]. Conversely, *L. plantarum* IS-10506, used in this study, accelerated MUC5AC expression in gastric ulcers by Day 5 when administered as preventive therapy prior to ketorolac induction. The immunomodulatory effects of bacterial interactions with the epithelial membrane offer a nutritional advantage for intestinal mucin polymers, especially secretory mucins since the majority of bacteria reside in the outer portion of the mucus layers [35–37].

CONCLUSIONS

The study reveals that *L. plantarum* IS-10506 has a noteworthy effect in promoting the healing of gastric ulcers, especially seen in the outcomes for groups K3. For group K3, which received the probiotic after ulcer induction by ketorolac, there was a marked improvement in the expression of MUC5AC, indicating a beneficial response in healing the gastric lining. In contrast, group K4, which was administered the probiotic before the ketorolac treatment, exhibited a quicker increase in MUC5AC levels, suggesting a preventive gastric ulcer. These insights suggest that *L. plantarum* IS-10506 could be valuable not only in recovering from gastric ulcer induced by COX inhibitors but also as a preventive strategy, bolstering the stomach's defenses before any damage occurs. The findings prescribe for the potential inclusion of probiotics as a strategic element in managing and safeguarding gastric health. Further research may focus on understanding the exact mechanisms of action, optimal dosing, and the potential translation of these findings into clinical practice for the benefit of patients suffering from NSAID-induced gastric ulcers.

REFERENCES

1. Fornai, M., Antonioli, L., Rocchina, C., Marco, T. & Blandizzi, C. Pathophysiology of gastric ulcer development and healing: molecular mechanisms and novel therapeutic options. in *Peptic ulcer disease* 113–142 (Jianyan Chai, 2011).
2. Laine, L., Takeuchi, K. & Tarnawski, A. Gastric mucosal defense and cytoprotection: bench to bedside. *Gastroenterology* **135**, 41–60 (2008).
3. Drini, M. Peptic ulcer disease and non-steroidal anti-inflammatory drugs. *Aust Prescr* **40**, 91 (2017).
4. Rodríguez-Silverio, J., Sánchez-Mendoza, M. E., Arrieta-Valencia, J., Rocha-Gonzalez, H. I. & Flores-Murrieta, F. J. Tizanidine increases antinociceptive effect and prevents gastric damage induced by ketorolac in the rat. *Drug Dev Res* **74**, 38–42 (2013).

5. Russo, R. *et al.* Ketogal: a derivative ketorolac molecule with minor ulcerogenic and renal toxicity. *Front Pharmacol* **8**, 757 (2017).
6. Johansson, M. E. V, Sjövall, H. & Hansson, G. C. The gastrointestinal mucus system in health and disease. *Nat Rev Gastroenterol Hepatol* **10**, 352–361 (2013).
7. Gomi, A. *et al.* Effect of Bifidobacterium bifidum BF-1 on gastric protection and mucin production in an acute gastric injury rat model. *J Dairy Sci* **96**, 832–837 (2013).
8. Nordman, H. *et al.* Gastric MUC5AC and MUC6 are large oligomeric mucins that differ in size, glycosylation and tissue distribution. *Biochemical Journal* **364**, 191–200 (2002).
9. Khoder, G., Al-Menhali, A. A., Al-Yassir, F. & Karam, S. M. Potential role of probiotics in the management of gastric ulcer. *Exp Ther Med* **12**, 3–17 (2016).
10. Hafez, M. M. Upregulation of intestinal mucin expression by the probiotic bacterium E. coli Nissle 1917. *Probiotics Antimicrob Proteins* **4**, 67–77 (2012).
11. Guli, M., Winarsih, S., Barlianto, W., Illiandri, O. & Sumarno, S. Mechanism of Lactobacillus reuteri Probiotic in Increasing Intestinal Mucosal Immune System. *Open Access Maced J Med Sci* **9**, 784–793 (2021).
12. Bermudez-Brito, M., Plaza-Díaz, J., Muñoz-Quezada, S., Gómez-Llorente, C. & Gil, A. Probiotic Mechanisms of Action. *Ann Nutr Metab* **61**, 160–174 (2012).
13. Surono, I., Verhoeven, J., Verbruggen, S. & Venema, K. Microencapsulation increases survival of the probiotic Lactobacillus plantarum IS-10506, but not Enterococcus faecium IS-27526 in a dynamic, computer-controlled in vitro model of the upper gastrointestinal tract. *J Appl Microbiol* **124**, 1604–1609 (2018).
14. Akuzawa, R., Miura, T. & Surono, I. S. Asian fermented milks. *Encyclopedia of Dairy Science* **2**, 507–511 (2011).
15. Umanets, A., Surono, I. S. & Venema, K. I am better than I look: genome based safety assessment of the probiotic Lactiplantibacillus plantarum IS-10506. *BMC Genomics* **24**, 518 (2023).
16. Dharmawan, J., Surono, I. S. & Kun, L. Y. Adhesion properties of indigenous dadih lactic acid bacteria on human intestinal mucosal surface. *Asian-Australas J Anim Sci* **19**, 751–755 (2006).
17. Pratiwi, F. *et al.* Lactobacillus plantarum IS-10506 Accelerates Healing of Gastric Injury Induced by Ketorolac in Wistar Rats. *Res J Pharm Technol* **16**, 308–313 (2023).
18. Wallace, J. L., McKnight, W., Reuter, B. K. & Vergnolle, N. NSAID-induced gastric damage in rats: requirement for inhibition of both cyclooxygenase 1 and 2. *Gastroenterology* **119**, 706–714 (2000).
19. Brune, K. & Patrignani, P. New insights into the use of currently available non-steroidal anti-inflammatory drugs. *J Pain Res* 105–118 (2015).
20. Wallace, J. L. NSAID gastropathy and enteropathy: distinct pathogenesis likely necessitates distinct prevention strategies. *Br J Pharmacol* **165**, 67–74 (2012).
21. Mills, J. C. & Shivdasani, R. A. Gastric epithelial stem cells. *Gastroenterology* **140**, 412–424 (2011).
22. Babu, S. D., Jayanthi, V., Devaraj, N., Reis, C. A. & Devaraj, H. Expression profile of mucins (MUC2, MUC5AC and MUC6) in Helicobacter pylori infected pre-neoplastic and neoplastic human gastric epithelium. *Mol Cancer* **5**, 1–7 (2006).
23. Carrato, C. *et al.* Differential apomucin expression in normal and neoplastic human gastrointestinal tissues. *Gastroenterology* **107**, 160–172 (1994).
24. De Bolós, C., Garrido, M. & Real, F. X. MUC6 apomucin shows a distinct normal tissue distribution that correlates with Lewis antigen expression in the human stomach. *Gastroenterology* **109**, 723–734 (1995).
25. Reis, C. A. *et al.* Immunohistochemical study of MUC5AC expression in human gastric carcinomas using a novel monoclonal antibody. *Int J Cancer* **74**, 112–121 (1997).
26. Nam, S. Y. *et al.* Gastric mucosal protection via enhancement of MUC5AC and MUC6 by geranylgeranylacetone. *Dig Dis Sci* **50**, 2110–2120 (2005).
27. Caballero-Franco, C., Keller, K., De Simone, C. & Chadee, K. The VSL# 3 probiotic formula induces mucin gene expression and secretion in colonic epithelial cells. *American Journal of Physiology-Gastrointestinal and Liver Physiology* **292**, G315–G322 (2007).
28. Khailova, L. *et al.* Bifidobacterium bifidum improves intestinal integrity in a rat model of necrotizing enterocolitis. *American Journal of Physiology-Gastrointestinal and Liver Physiology* **297**, G940–G949 (2009).
29. Moon, G. *et al.* Prophylactic effect of Lactobacillus GG in animal colitis and its effect on cytokine secretion and mucin gene expressions. *The Korean Journal of Gastroenterology* 234–245 (2004).
30. Uribe, G. *et al.* Lactobacillus rhamnosus GG increases cyclooxygenase-2 expression and prostaglandin E2 secretion in colonic myofibroblasts via a MyD88-dependent mechanism during homeostasis. *Cell Microbiol* **20**, e12871 (2018).
31. Morteau, O. Prostaglandins and inflammation: the cyclooxygenase controversy. *Inflammation* 67–81 (2001).
32. Ji, J. & Yang, H. Using probiotics as supplementation for Helicobacter pylori antibiotic therapy. *Int J Mol Sci* **21**, 1136 (2020).
33. Suez, J. *et al.* Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. *Cell* **174**, 1406–1423 (2018).
34. Uchida, M., Shimizu, K. & Kurakazu, K. Yogurt containing Lactobacillus gasseri OLL 2716 (LG21 yogurt) accelerated the healing of acetic acid-induced gastric ulcer in rats. *Biosci Biotechnol Biochem* **74**, 1891–1894 (2010).
35. Carrington, S. D., Clyne, M., Reid, C. J., FitzPatrick, E. & Corfield, A. P. Microbial interaction with mucus and mucins. in *Microbial glycobiology* 655–671 (Elsevier, 2010).
36. Johansson, M. E. V *et al.* The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. *Proceedings of the national academy of sciences* **105**, 15064–15069 (2008).
37. Sonnenburg, J. L., Angenent, L. T. & Gordon, J. I. Getting a grip on things: how do communities of bacterial symbionts become established in our intestine? *Nat Immunol* **5**, 569–573 (2004).

Cite this article: Andarsini MR, Darma A, Athiyyah AF, Sumitro KR, Ranuh RG, Pratiwi F, Riawan W, et al. Effect of *Lactiplantibacillus plantarum* IS-10506 on Accelerating Repair of Ketorolac-Induced Gastric Ulcers in Wistar Rats. Pharmacogn J. 2024;16(1): 181-185.