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Effects of *Lactobacillus plantarum* IS-10506 on gastric protective mucosal factors: an ibuprofen-induced gastric mucosal injury



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ABSTRACT

Background: Gastric mucosal protective factor plays an important roles in gastric homeostasis between mucosal injury and mucosal repair. Previous study implicated probiotics in the repair of the intestinal mucosa, while probiotic role in gastric mucosa remains poorly understood. This study aims to determine the role of probiotic *L. plantarum* IS-10506 in gastric protective mucosal factors by examining the expression of cyclooxygenase-1 (COX-1), COX-2, prostaglandin E2 (PGE2), and gastric mucus production (Mucin 5AC/ MUC5AC) by surface mucous cells as gastric mucosal protective factors.

Methods: Twenty-seven male Wistar rats (*Rattus norvegicus*) were divided into 3 groups, ie. control, curative and preventive group. Ibuprofen 300mg/kgBW were given to all groups to induce gastric injury, while *Lactobacillus plantarum* IS-10506 1x10⁹CFU/day were given into the curative (5 days) and preventive (12 days) groups. Antrum tissue with primary monoclonal antibodies againts COX-1, COX-2, PGE2, and MUC5AC were examined in the day -1, -3, and -5 after necropsy.

Results: Number of cells expressed COX-1, COX-2, PGE2 and MUC5AC in curative and preventive groups were significantly higher than control group. *L. plantarum* IS-10506 showed its efficacy in gastric mucosal repair on third day in the curative group and on first day in the preventive group. *L. plantarum* IS-10506 probiotic plays a role in gastric protective mucosal factors by promoting cell expression of COX-1, PGE2, and MUC5AC. In addition, it has been determined that *L. plantarum* IS-10506 inhibits COX-2 expression, that may lead to minimize the inflammatory conditions and a deterioration of the gastric mucosal environment.

Conclusion: *Lactobacillus plantarum* IS-10506 can prevent ibuprofen-induced antral mucosal damage through gastric protective mucosal factors.

Keywords: *Lactobacillus plantarum* IS-10506, gastric, COX-1, COX-2, PGE2, MUC5AC.

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INTRODUCTION

Gastric mucosal integrity plays an important role to keep gastric homeostatic. Mucosal injury, mucosal healing, and various mucosal protective factors are in an equilibrium position under physiological condition.^{1,2} The main gastric mucosal protective factor is the presence of mucus-buffers-phospholipid layer (Mucin 5AC/ MUC5AC) as pre-epithelial barrier which is enhanced by prostaglandins and continuously renewed layer of surface epithelial cells as the second line of mucosal defense.² Prostaglandins are produced from arachidonic acid metabolism through the cyclooxygenase (COX) enzymes. In

gaster, prostaglandin E2 (PGE2) play an important role to maintain mucosal integrity by upregulating mucosal blood flow and stimulating mucus production that cover gastric epithelial layer against noxious substances.¹⁻³ Ibuprofen is one of non-selective non-steroidal anti-inflammatory drug (NSAID) that well known as common cause of gastric mucosal damage.⁴⁻⁶ NSAID plays an important role as exogenous aggressive factor in gastric mucosal injury by inhibiting prostaglandin synthesis, thereby reducing mucus production, bicarbonate secretion, and mucosal blood flow.²

Probiotics are defined as microorganisms that provide therapeutic benefits to the host when given

appropriately.⁷ Previous research has implicated probiotics in the repair of the gastrointestinal mucosa.⁴ This study chooses *Lactobacillus plantarum* IS-10506 as it has very stable viability in phosphate buffers solution (pH7) in 48 hours compared to *L. acidophilus* and *L. rhamnosus* GG.⁸ Previous study on *L. plantarum* IS-10506 has also shown the regeneration capabilities in the intestinal brush border⁹ and ileum surface structure¹⁰ and activate the intestinal stem cell in a rodent model.¹¹ While these finding suggest *L. plantarum* IS-10506 provide therapeutic benefit in intestinal mucosa, it's role in gastric mucosa remains poorly understood. This study aims to determine the role of *L. plantarum* IS-10506 in ibuprofen-induced

gastric mucosal injury by examining the cell expression of COX-1, COX-2, PGE2, and MUC5AC as mucosal protective factors.

13 MATERIALS AND METHODS

Samples and study design

A randomized controlled trial study used male rats *Rattus norvegicus* Wistar strain, aged 12 weeks and each weighing between 200-250 grams from The Integrated Research and Testing Laboratory, Universitas Gadjah Mada. Twenty-seven rats were divided into 3 treatment groups, i) control, ii) curative and iii) preventive group and each group consists of 9 rats. Ethical clearance of this study was approved by the Ethical Committee of Faculty of Veterinary Medicine, Universitas Airlangga (No. 2.KE.022.03.2021).

Ibuprofen

Ibuprofen were given at dose 300 mg/kgBW, diluted with 1 ml aquadest in a 1:1 ratio to induce gastric mucosal injury. On day-0, ibuprofen will be administered to all groups through an oral gavage. For control group, distilled water was given for 5 days after being given ibuprofen (day 1 – 5).

Probiotic

Microencapsulated *Lactobacillus plantarum* IS-10506 (GeneBank accession n° DQ860148) powder in 1% skimmed media given by oral gavage at a dose of 1×10^9 CFU/day. This probiotic will be dissolved in 1.5 ml of sterile water once daily. For the curative group, probiotics will be given for 5 days after being given ibuprofen (day 1 – 5). While for preventive group, probiotic given for total 12 days from 6 days before until 5 days after being given ibuprofen (day [-6] – 5).

Antrum tissue collection

All rats from all groups were surgically dissected under ether anesthesia and sacrificed on day-1, -3 and -5 after ibuprofen administered. The antrum tissue sections were excised and cleaned then fixed with a 10% formalin buffer solution for histopathology preparations. Paraffin blocks is carried out at the PathologyAnatomy Laboratory, Faculty of

Medicine, Universitas Airlangga.

Immunohistochemistry

Paraffin blocks containing antrum gastric tissue were sliced in 4 μ m, deparaffinized and followed by dehydration, clearing and embedding. Obtained antrum tissues were probed with primary monoclonal antibodies against COX-1 (SC-19998, Santa Cruz Biotechnology, California, USA), COX-2 (SC-19999, Santa Cruz Biotechnology, California, USA), PGE2 (SC-514224, Santa Cruz Biotechnology, California, USA) and MUC5AC (45M1, Thermo Fisher Scientific, Massachusetts, USA). Immunopositive cells were counted by the average number of cells expressing antibody from 20 random fields at 1000 \times magnification. Histological samples were observed and counted by one independent examiner under a light microscope (CX21; Olympus, Tokyo, Japan) and photographed using a Nikon E100 microscope (Nikon Instruments Inc., Tokyo, Japan) in the Biomolecular Biochemistry Laboratory, Department of Biomolecular Biochemistry, Faculty of Medicine, Universitas Brawijaya.

18 Statistical Analysis

Data were presented as mean \pm standard deviation (SD) by bar chart. Statistical analysis was done by using Kruskal Wallis and Mann-Whitney U test (as the data was not normally distributed) to find differences between groups treatment on each day (day-1, -3 and -5), with $p < 0.05$ considered statistically significant.

RESULTS

Cyclooxygenase (COXs)

Both probiotic groups (curative and preventive) had an upward trend in COX-1 expression from the 1st to 5th day. On the contrary, ibuprofen group showed the lowest COX-1 expression from the 1st to 5th day between all groups. The curative group showed significantly higher COX-1 expression compared to the ibuprofen group on the 3rd and 5th day, while the preventive group already showed the difference from the 1st day (Fig. 1A). Contrast result was found in COX-2 expression between groups. Probiotic groups show downward trend in COX-2 expression from the 1st to 5th

day. Meanwhile ibuprofen group show highest and upward trend in COX-2 expression. On the 3rd and 5th day, COX-2 expression was significantly lower in the curative and preventive groups compared to the ibuprofen group (Fig. 2A). The immunohistochemical examination of COX-1 and COX-2 cell expression was figured in Fig. 1B and 2B. The COX-1/COX-2 ratio is determined to summarize the role of probiotics in cyclooxygenase expression. Both probiotic groups showed upward trend in COX-1/COX-2 ratio expression from the 1st to 5th day. On the 3rd and 5th day, the expression of the COX-1/COX-2 ratio was significantly higher in the curative group than in the ibuprofen group. The preventive group showed significantly higher COX-1/COX-2 ratio expression than the ibuprofen group on the 1st, 3rd and 5th day (Fig. 3). These findings suggest that the protective mechanisms through COXs may have began earlier in the preventive group than in the curative group.

Prostaglandin E2 (PGE2)

Ibuprofen caused a decreased expression of PGE2 from the 1st to 5th day while probiotic groups shows an upward trend. Linear to the COX-1/COX-2 ratio, the curative group showed significantly higher PGE2 expression than the ibuprofen group on the 3rd and 5th day. Meanwhile, the preventive group showed significantly higher PGE2 expression compared to the ibuprofen group from the 1st to 5th day (Fig. 4A). The immunohistochemical examination of PGE2 cell expression was figured in Fig. 4B.

Mucin 5AC (MUC5AC)

Probiotics groups show an upward trend of MUC5AC expression while ibuprofen shows a downtrend. Relevant to the COXs ratio and PGE2 result, the curative group showed significantly higher MUC5AC expression than the ibuprofen group on the 3rd and 5th day. PGE2 expression was significantly higher in the preventive group than in the ibuprofen group on the 1st, 3rd and 5th day (Fig. 5A). The immunohistochemical examination of MUC5AC cell expression was figured in Fig. 5B.

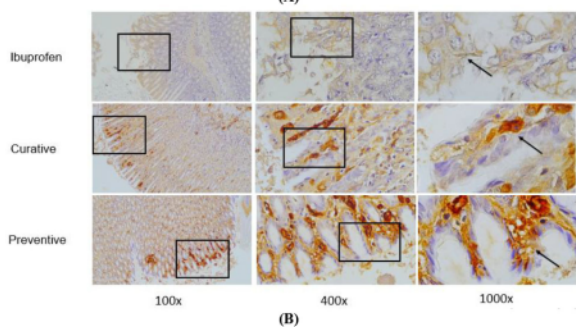
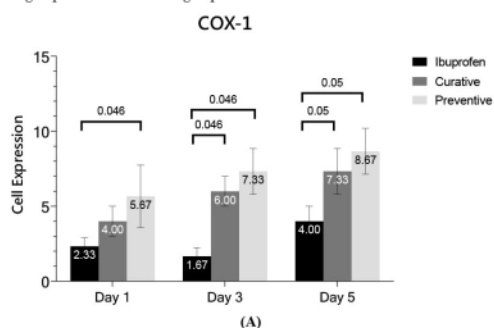


Figure 1. A. Effect of ibuprofen and probiotic on COX-1; mean \pm standard deviation (SD) B. Immunohistochemical examination of COX-1 cell expression with 100x, 400x, and 1000x magnification. Brown colored tissue (marked by arrow) shows cell parts that express COX-1 in ibuprofen, curative and preventive groups.

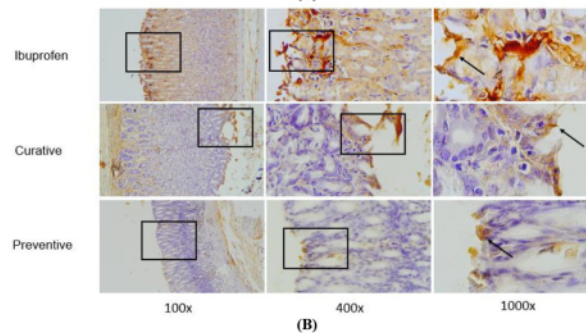
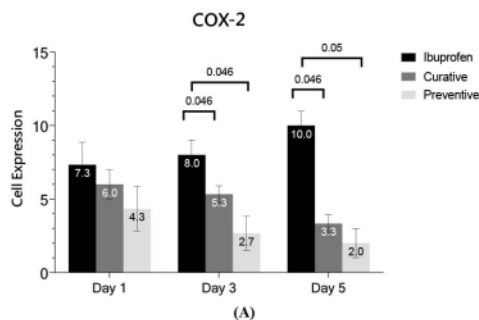


Figure 2. A. Effect of ibuprofen and probiotic on COX-2; mean \pm standard deviation (SD) B. Immunohistochemical examination of COX-2 cell expression with 100x, 400x, and 1000x magnification. Brown colored tissue (marked by arrow) shows cell parts that express COX-2 in ibuprofen, curative and preventive groups.

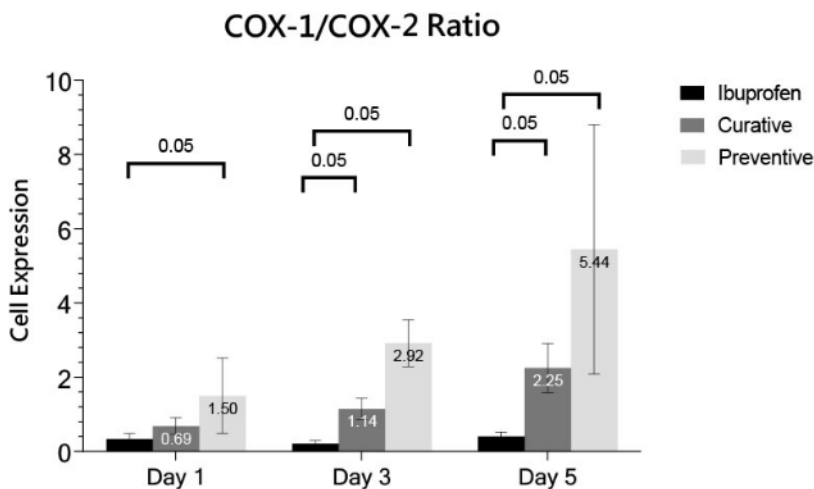


Figure 3. Effect of ibuprofen and probiotic on COX-1/COX-2 ratio expression; mean \pm standard deviation (SD).

DISCUSSION

Our study found that probiotic administration increases the expression of COX-1 and PGE2 compared to the control

group. Increased PGE-2 expression of gastric mucosa in curative and preventive is linear with increased COX-1 expression in each group, showing that in this condition

most of the PGE-2 synthesized by COX-1 as a protective factor of gastric mucous. There have been many studies on the effect of probiotics on the production of PGE2, which plays a role in the healing process of gastric injury, however knowledge of the effects of *L. plantarum* on PGE2 as a single agent is still limited. A previous study has shown that *L. rhamnosus* and *E. coli* have a therapeutic effect on gastric injury by increasing PGE2 secretion.⁴

This study also determined that probiotics decrease COX-2, that can lead to anti-inflammatory effect. Prior study by Han et al. show similar result that *L. plantarum* was linked to significant decrease in expression of COX-2 compared to lipopolysaccharide control. *L. plantarum* also show higher decrease in COX-2 expression compared to *L. rhamnosus* although failed to show statistically significant.¹² Our study also support a previous study by J. M. Otte et al. that found reduction in intestinal COX-2 expression with VSL3 probiotic which

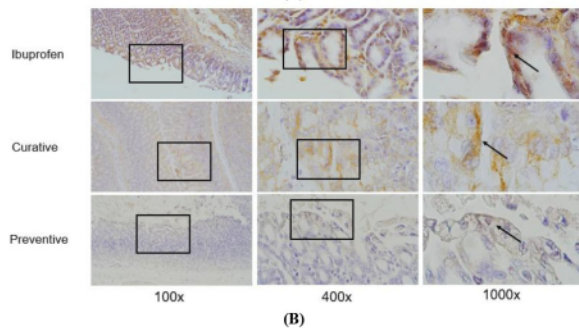
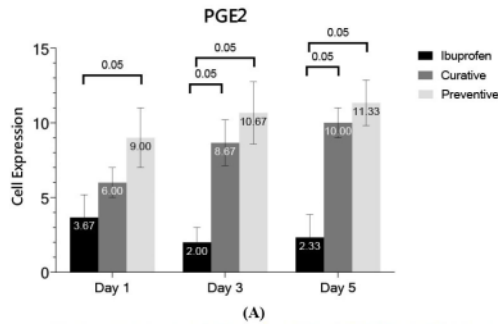


Figure 4. A. Effect of ibuprofen and probiotic on PGE2 expression; mean \pm standard deviation (SD) B. Immunohistochemical examination of PGE2 cell expression with 100x, 400x, and 1000x magnification. Brown colored tissue (marked by arrow) shows cell parts that express PGE2 in ibuprofen, curative and preventive groups.

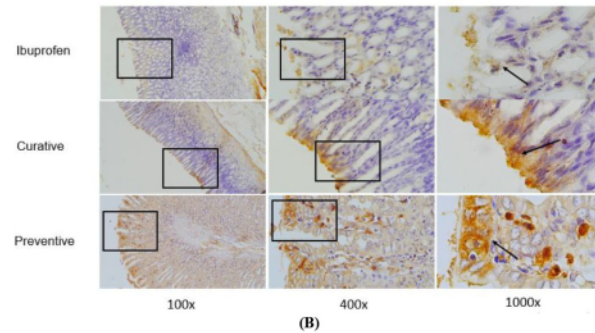
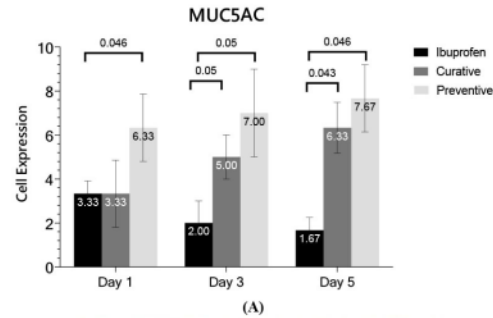


Figure 5. A. Effect of ibuprofen and probiotic on MUC5AC expression; mean \pm standard deviation (SD) B. Immunohistochemical examination of MUC5AC cell expression with 100x, 400x, and 1000x magnification. Brown colored tissue (marked by arrow) shows cell parts that express MUC5AC in ibuprofen, curative and preventive groups.

contains eight different microorganism strains, including *L. plantarum*. This study also found that VSL3 reduces inflammatory agent (gastrin and TNF- α).¹³ *Bifidobacterium lactis* share more specific result by increasing COX-1 expression while simultaneously decreasing COX-2 expression.¹⁴

Gastric mucous plays a protective role by sheltering the gastric epithelial cells from acid and noxious agents.⁴ This study shows that probiotic treatment has a significant role in MUC5AC expression increase. This finding supports previous study that found MUC5AC expression was slightly elevated in VSL3-treated animals, although not statistically significant.¹⁵ In addition, we found a linear result between COX-1/COX-2 ratio, PGE2 and MUC5AC expression, showing that COX-1-generated PGE2 plays a part in MUC5AC secretion. This finding could provide additional insight into previous research indicating that

MUC5AC is primarily activated by the COX-2/PGE2 pathway.¹⁵⁻¹⁷

The interesting finding in this study is that there are significant differences in COX-1, COX-2, PGE-2, and MUC5AC expression between the ibuprofen vs curative group in the 3rd and 5th day and ibuprofen vs preventive group on the 1st, 3rd and 5th day. These results indicate that curative probiotic treatment started showing its efficacy from the 3rd day while preventive treatment provides an earlier onset of efficacy on the 1st day of the study. Khoder et al summarize probiotics' prophylactic and therapeutic effects in gastric ulcers. Probiotics protect the integrity of the gastric mucosal barrier by upregulating prostaglandin E2, mucous secretion, and downregulating apoptosis. Probiotics could also accelerate healing in gastric ulcers by increasing the generation of prostaglandin E2. Pre-treatment with probiotics upregulates MUC5AC gene

expression thus increasing gastric mucous production by surface mucous cells.⁴

The limitation of this study is that we did not measure the level of COX and other markers produced but by the cells expression using immunohistochemistry methods. As a result, additional studies that include the assessment of marker levels might be necessary to support our findings.

CONCLUSION

The findings of our study show that *L. plantarum* IS-10506 plays a role in gastric mucosal protective factors by increasing cell expression of COX1, PGE2, and MUC5AC. In addition, it has been determined that *L. plantarum* IS-10506 inhibits COX2 expression, that may lead to minimize the inflammatory conditions and a deterioration of the gastric mucosal environment.

DISCLOSURE

Conflict Of Interest

All authors declare no conflicts of interest.

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Author Contribution

Conception: AD, IS, SMS; design: AD, AFA, RR, IS, SMS; Literature search: AD, KRS, AFA, RR, IS, SMS; Analysis and interpretation of the data: AD, WR, KRS, MFQ; Manuscript preparation: AD, WR, KRS, AFA; Manuscript editing: AD, KRS, AFA, RR, MFQ; Manuscript review: all authors.

ETHICAL CLEARANCE

Ethical clearance of this study was approved by the Ethical Committee of Faculty of Veterinary Medicine, Universitas Airlangga (No. 2.KE.022.03.2021).

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REFERENCES

1. Oncel S, Basson MD. Gut homeostasis, injury, and healing: New therapeutic targets. *World*

- Journal of Gastroenterology. 2022;28:1725–1750. <https://doi.org/10.3748/wjg.v28.i17.1725>
2. Yandrapu H, Sarosiek J. Protective Factors of the Gastric and Duodenal Mucosa: An Overview. *Curr Gastroenterol Rep*. 2015;17:1–8. <https://doi.org/10.1007/s11894-015-0452-2>
3. Phillipson M, Johansson MEV, Henriksnäs J, Petersson J, Gendler SJ, Sandler S, et al. The gastric mucus layers: Constituents and regulation of accumulation. *Am J Physiol Gastrointest Liver Physiol*. 2008;295:806–812. <https://doi.org/10.1152/ajpgi.90252.2008>
4. Khoder G, Al-Menhali A, Al-Yassir F, Karam S. Potential role of probiotics in the management of gastric ulcer (Review). *Exp Ther Med*. 2016;12:3–17. <https://doi.org/10.3892/etm.2016.3293>
5. Watanabe T, Fujiwara Y, Chan FKL. Current knowledge on non-steroidal anti-inflammatory drug-induced small-bowel damage: a comprehensive review. *J Gastroenterol*. 2020;55:481–495. <https://doi.org/10.1007/s00535-019-01657-8>
6. Ha MW, Paek SM. Recent advances in the synthesis of ibuprofen and naproxen. *Molecules*. 2021;26:4792. <https://doi.org/10.3390/molecules26164792>
7. Iqbal Z, Ahmed S, Tabassum N, Bhattacharya R, Bose D. Role of probiotics in prevention and treatment of enteric infections: a comprehensive review. *3 Biotech*. 2021;11:1–26. <https://doi.org/10.1007/s13205-021-02796-7>
8. Suroño IS. In vitro probiotic properties of indigenous dadih lactic acid bacteria. *Asian-Australas J Anim Sci*. 2003;16:726–731. <https://doi.org/10.5713/ajas.2003.726>
9. Ranuh RG, Athiyah AF, Darma A, Riawan W, Suroño IS, Sandra F, et al. Lactobacillus plantarum IS-20506 probiotic restores galectin-4 and myosin-1a expressions in duodenum, jejunum and ileum of lipopolysaccharide-induced rats. *Indonesian Biomedical Journal*. 2020;12:283–287. <https://doi.org/10.18585/inabj.v12i3.1098>
10. Athiyah AF, Darma A, Ranuh RG, Riawan W, Sudiana IK, Suroño IS, et al. The effects of lactobacillus plantarum IS-10506 on accelerating the regeneration of the intestinal mucosa structure examined by the scanning electron microscope. *Carpathian Journal of Food Science and Technology*. 2019;10:11–18.
11. Athiyah AF, Darma A, Ranuh R, Riawan W, Endaryanto A, Rantam FA, et al. Lactobacillus plantarum IS-10506 activates intestinal stem cells in a rodent model. *Benef Microbes*. 2018;9:755–760. <https://doi.org/10.3920/BM2017.0118>
12. Han KJ, Lee JE, Lee NK, Paik HD. Antioxidant and Anti-inflammatory effect of probiotic lactobacillus plantarum KU15149 derived from Korean homemade Diced-radish kimchi. *J Microbiol Biotechnol*. 2020;30:591–598. <https://doi.org/10.4014/jmb.2002.02052>
13. Otte JM, Mahjuri-Namari R, Brand S, Werner I, Schmidt WE, Schmitz F. Probiotics regulate the expression of COX-2 in intestinal epithelial cells. *Nutr Cancer*. 2009;61:103–113. <https://doi.org/10.1080/01635580802372625>
14. Nurmi JT, Puolakkainen PA, Rautonen NE. Bifidobacterium lactis sp. 420 up-regulates cyclooxygenase (Cox)-1 and down-regulates Cox-2 gene expression in a caco-2 cell culture model. *Nutr Cancer*. 2005;51:83–92. https://doi.org/10.1207/s15327914nc5101_12
15. Dharmani P, de Simone C, Chadee K. The Probiotic Mixture VSL#3 Accelerates Gastric Ulcer Healing by Stimulating Vascular Endothelial Growth Factor. *PLoS One*. 2013;8:e58671. <https://doi.org/10.1371/journal.pone.0058671>
16. Gray T, Nettesheim P, Loftin C, Koo JS, Bonner J, Peddada S, et al. Interleukin-1 β -induced mucin production in human airway epithelium is mediated by cyclooxygenase-2, prostaglandin E2 receptors, and cyclic AMP-protein kinase A signaling. *Mol Pharmacol*. 2004;66:337–346. <https://doi.org/10.1124/mol.66.2.337>
17. Li Y, Song J, Yu H, Wu S. PGE2 induces MUC2 and MUC5AC expression in human intrahepatic biliary epithelial cells via EP4/p38MAPK activation. *Ann Hepatol*. 2013;12:479–486. [http://doi.org/10.1016/S1665-2681\(19\)31012-9](http://doi.org/10.1016/S1665-2681(19)31012-9)



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22 Olasupo Stephen Adeniyi, Benjamin O Emikpe, SAMUEL OLALEYE. "Accelerated gastric ulcer healing in thyroxine-treated rats; roles of gastric acid, mucus and inflammatory response", *Canadian Journal of Physiology and Pharmacology*, 2018
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23 P Bhandari. "Mucosal expression of cyclooxygenase isoforms 1 and 2 is increased

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