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Submission date: 07-Apr-2023 10:56AM (UTC+0800)
Submission ID: 2058086581
File name: Lactobacillus_plantarum.pdf (3.04M)
Word count: 790
Character count: 4407

ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

RESEARCH ARTICLE

Lactobacillus plantarum IS-10506 Accelerates Healing of Gastric Injury Induced by Ketorolac in Wistar Rats

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ABSTRACT:

Gastric injury is an event that often occurs due to many factors, such as the use of drugs, stress factors, infections, chemicals, etc. The use of histamin 2(H2) receptor antagonist drugs and pump inhibitors have become the choice for gastric injury treatment so far and requires a relatively long time. The widespread use of probiotics has been shown to affect the healing process of digestive tract disorders, for example in the small intestine. This study aimed to investigate the effect of *Lactobacillus plantarum*IS-10506 in acceleratingthe healing of gastric injury induced by ketorolac in the rat. The experimental study used 64 Wistar rats divided into 4 groups, group 1 (control), group 2(ketorolac administration), group 3 (ketorolac and probiotic administration), and group 4(preventive treatment with probiotic before, ketorolac administration, and treatment with probiotic). Each group was divided into 4 subgroups based on the day of sacrifice, days 1, 5, 7, 10. The healing of gastric injury evaluating by epithelial defects improvement and fibroblast cells by hematoxylin and eosin (HE) staining.The group induced by ketorolac (group 2) showed the highest epithelial defect score (p=0.048) on day 1. The repair of the epithelial defect in group 3 and group 4 were significantly increased on day 5, while group 2remains defectiveon day 5(p=0.019). Fibroblast cells of groups 3 and 4 decreased significantly more than others on day 10(p=0.024). *Lactobacillus plantarum* IS-10506 influences the healing acceleration of gastric injury by ketorolac by enhancing epithelial regenerationand fibroblast cells.

KEYWORDS: Gastric injury, ketorolac, *Lactobacillus plantarum* IS-10506, Wistar rat.

INTRODUCTION:

Gastric injury incidence can happen caused by many factors, such as prolonged use of nonsteroidal anti-inflammatory drugs (NSAID).[1] Ketorolac is a well-researched NSAID with anti-inflammatory, antipyretic and analgesic effects that is frequently recommended, whichcan inhibit the activity of the prostaglandin (PG) biosynthetic enzymes, the cyclooxygenase (COX) isoforms 1 and 2.[2,3] The healing process of gastric injury includes cell proliferation, migration, re-epithelialization, granulation tissue formation, angiogenesis, and interactions between various cells and extracellular matrix, all of which result in scar tissue formation and tissue remodelling, involving the role of fibroblasts in the early stages.[4]

Received on 24.07.2022 Modified on 14.09.2022
Accepted on 04.11.2022
Research J. Pharm. and Tech 2023; 16(1):307-313.
DOI: 10.52711/0974-360X.2023.00055

The gastric first defence mechanism is the gastric mucosal lining, composed of glycosylated proteins that form a gel layer of the gastric mucous membrane through the gene encoding mucin.[5]

Gastric acid reduction and/or neutralization were the main goals of pharmaceutical care of gastric injury.[6] The treatment of gastric injury has been using proton pump inhibitor (PPI) and other drugs.[7] The etiology of stress-induced gastric ulcers has also been linked to endogenous histamine production and mast cell discharge from the stomach mucosa, hence H2 receptor antagonists, such as ranitidine were used.[8] The use of probiotics is currently being developed as an alternative therapy for gastric injury therapy, considering that there have been many benefits of probiotics in many types of diseases.[9] *Lactobacillus plantarum* is a widespread lactic acid bacterium commonly found infermented foods as well as in the human gastrointestinal tract. In some strains of *L.plantarum* the ability to survive along the

human gastrointestinal tract has been proved aside from their capacity to adhere to the epithelium cells where benefic actions can take place.[10] The study held by Athiyyah et.al. in 2019 showed the benefit of *Lactobacillus plantarum* IS-10506 (*L. plantarum* IS-10506) has been shown in accelerating the regeneration of the intestinal mucosal structure.[11] The study held by Ranuh et.al, in 2020 showed that L. *plantarum* IS-10506 showed a significant role in intestinal stem cells and intestinal mucosal barrier integrity.[12]

Our present study examined the effects *Lactobacillus plantarum*IS-10506 in accelerating healing of gastric injury induced by ketorolac in the rat.

MATERIAL AND METHODS:

Probiotic:

Microencapsulated *Lactobacillus plantarum* IS-10506 (GeneBank accession n° DQ860148) was dissolved in 1.5ml of sterile water and administered daily, through a gastric tube, at an of dose 2.86 x 10^{10} CFU/day. The probiotic was given to group 3 after induced ketorolac. For group 4, the probiotic was given 6 days before inducing ketorolac, and the probiotic was given after inducing ketorolac. Probiotic (*Lactobacillus plantarum* IS-10506 2,86x 10^{10} CFU equal 1gram.

Ketorolac:

Ketorolac with a dosage of 30mg/kg body weightwas given one day, and the rat fasted for 6-8 hours before (Ketorolac Trometamol, No. Reg: DKL 0604425417A1, Dankos Farma, Indonesia) suspended in sterile water through gavage then treated with distilled water daily on the following days. On day 1, 5, 7, and 10 after being induced with one day of ketorolac 30mg/kg body weight administration, rats were sacrificed, and the ngastrict issue was collected.

Animal Preparation:

Male Wistar rats (n = 64, 12weeks old, approximately 150-250g obtained from Yogyakarta Agricultural Institute) were housed in 16cages (fourpercage) on a 12 hours:12 hours light/dark cycle. All animals were acclimated to their environment for 1 week and had ad libitum access to water and a standard rodent chow diet. Rats were routinely monitored for body weight (BW). The rats were deprived of food, but notwater,for 6-8 hours beforean experiment. After 7 days of acclimatization, sixty four *Wistar* rats were equally assigned into 4 experimental main groups (group 1 was a control group, consisting of 16 rats, given sterile water; group 2 was ketorolac induced group, which consisted of 16 rats; group 3 was ketorolac induced group, continued with probiotic treatment, consisted of 16 rats; and group 4 was probiotic preventive continued with ketorolac induced and continued with probiotic treatment, consisted of 16 rats). Group 1 as control group and groups 2, 3, 4 were experimental groups consisting of 16 rats divide into 4 sub-group according to the day of sacrifice, days 1, 5, 7 and 10, that each day consist of 4 rats. The control group consisted of 16 rats who were treated with distilled water daily througha gastric tube. This study received ethical approval from the Animal Careand Use Committee (ACUC) of the Veterinary Medicine School in Indonesia

Measurement of Gastric Injury:

The measurement of gastric injury using epithelial defectsscoreis based on the Histology Activity Index (HAI) score by Roger's criteria. The stomachs were removed, inflated by injecting 10ml of saline, immersed in 1% formalin for 1 hour to fix the gastric tissue, and opened along the greater curvature. The epithelial defect, epithelial reparation, and fibroblast cellswere scored by semiquantitative according to Roger's criteriaby anobserver unaware of the treatments.

Histology:

The gastric injury and healing were examined with HEstains under a microscope, either with fibroblast cells. The animals were euthanized after the drug administration under ketamine anaesthesia, and the stomachs were excised, immersed in 10% neutralized formalin, and embedded in paraffin. The sections (8mm) were cutusinga microtome and stained with HE. The epithelial defect score represented the gastric injury, with the scoring system according to Roger's criteria. The fibroblast cells were examined using the semiquantitative examination.

StatisticalAnalysis:

The statistical analysis used descriptive analysis to determine the description of gastric injury, healing of gastric injury by epithelial repair and fibroblast cells. Statistical test with ANOVA for data with normal distribution, and Kruskal Wallis and Mann-Whitney statistical test used for data with the abnormal distribution, with $p<0,05$ being significant.

RESULTS:

Through random allocation into 4 groups (control and treatment) and screening before treatment with inclusion criteria, namely rats aged 12 weeks and male sex with body weight 180grams – 200grams and exclusion criteria were animals within the observation period, the animal suffers from the illness, which can be seen from changes in animal behaviour (changes in eating/drinking patterns, animal activities) and other important clinical signs (weight loss, breathing patterns, diarrhoea, vomiting, etc.), the animals under observation die either due to physical and mental stress, damage to organs or tissues occurred during sampling. During the study,

there was 1 rat died for each group.

Gastric Injury Microscopic Examination:

The degree of gastric injury was assessed based on the method*histological activity index* (HAI) according to Rogers, 2012 which is modified with the value of the criteria has a vulnerability, where a score of 0-4 (0 = no abnormality entire visual field of view, 1 = abnormality <25% of the entire visual fieldof view, 2 = 25%-50% abnormality of the entire field of view, 3 = abnormalities 50% - 75% of the entire visual field of view, 4 = abnormalities > 75% of the entire field of view).[13] From the results of the microscopic picture of the gastric injuryhealing process on day 1 and day 10, it can be seen in the image below.

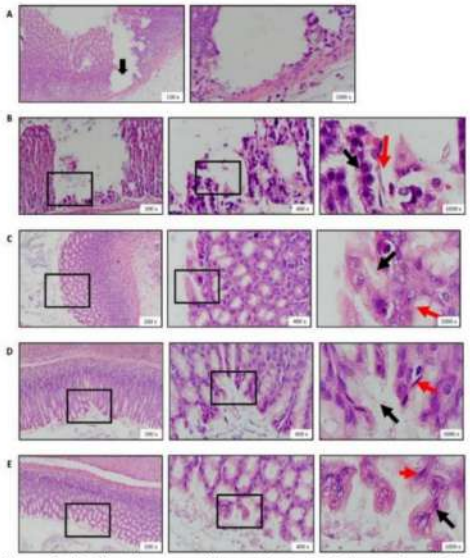

Figure 1. A) Gastric mucosal layer in group 2 (ketorolac induce) on examination day 1 with HE stains.

The figure showed the defect epithelial layer on day 1 after ketorolac was induced. The black row showed the epithelial defect. B) Gastric mucosal layer in group 2 (ketorolac induce) on examination day 10 with HE stains. The repair of the epithelial layer was still minimal. Black arrows indicate gastric and mucosal epithelial lining injury. Red arrows showed fibroblast cells. C) Gastric mucosal layer in the control group (group 1) on examination day 10 with HE stains. Visible epithelial layer intact, no injury found. Black arrows indicate an intact gastric and mucosal epithelial layer.Red arrows showed fibroblast cells. D) Gastric mucosal layer in group 3 (exposure to ketorolac-probiotics) on examination day 10 with HE stains. The epithelial layer injury that did not penetrate the submucosa area was seen; the epithelial layer healing was seen. Black arrows indicate gastric and mucosal epithelial lining injury. Red arrows showed fibroblast cells. E) Gastric mucosal layer in group 4 (probiotic-ketorolac-probiotic exposure) on examination day 10 with HE stains. Visible epithelial and mucosal layers are intact. Black arrows indicate gastric and mucosal epithelial layers. Red arrows showed fibroblast cells.

Description of the status of epithelial damage to the gastric mucosa after treatment between the control group 1 and the treatment group 2, 3, 4) in Wistar rats sacrificed on day 1, day 5, day 7, and day 10 are listed in table 1 below.

Table 1. Comparison of epithelial damage (gastricinjury between groups)

Group	Day			
	Day 1 (Mean ± SD)	Day 5 (Mean ± SD)	Day 7 (Mean ± SD)	Day 10 (Mean ± SD)
1	0 [a]	0 [a]	0 [a]	0
2	3.33 ± 1,155 [b]	3.67 ± 0.577 [c]	3 ± 1 [c]	2 ± 1
3	2.33 ± 0.577 [b]	1.33 ± 0.577 [b]	1.33 ± 0.577 [bc]	1.33±0.577
4	2.33 ± 0.577 [b]	1.33 ± 0.577 [b]	1 ± 0 [b]	1.33±0.577
p value	0.048*	0.019*	0.018*	0.055

*Significant difference in p<0.05 based on the Kruskall-Wallis test
[a,b,c]The same superscript shows results that are not significantly different based on the Mann Whitney test.

Based on the results, epithelial defect scores in group 2 were seen to be highest on day 5 after exposure to ketorolac. Epithelial defect scores showed the lowest values on day 5 in both groups 3 and 4, group 4 showed the lowest values of epithelial defects on day 7.

Table 2: Healing of gastric injury by looking at the fibroblast cells

Group	Day			
	Day 1 (Mean ± SD)	Day 5 (Mean ± SD)	Day 7 (Mean ± SD)	Day 10 (Mean ± SD)
1	4 ± 1	4.67±2.517	4 ± 1	5.33 ± 1,528 [b]
2	8±1.732	9±1.732	8.67±1.528	11.33 ± 1,528 [b]
3	6.33±1.528	5±1	2.67 ± 0.577	3 ± 1 [ab]
4	5.67±1.528	3.67±1.528	3.33±1.528	2.33 ± 1 [a]
p value	0.089	0.071	0.052	0.024*

*Significant difference in p<0.05 based on Kruskall Wallis test
[ab]The same results show that the results are not significantly different based on the Mann Whitney test

Based on the results it is known that group 1 is not significantly different from group 2 and group 3 but significantly different from group 4. Group 2 is significantly different from group 4 but not different from group 3, and group 3 is not significantly different from group 2 and group 4. Examination on day 1, day 5,

and day 7 had a p-value > 0.05, which means that there was no significant difference between groups. It can be seen that the expression of fibroblast cells as an expression of tissue damage was seen to have the highest value in each group on day 1. In groups 3 and 4, fibroblast cells began to decrease, indicating healing on day 5, and fibroblastcells decreased from day 7 to day 10. However, the expression value of fibroblasts increased every day in group 2. This showed an increase in gastric ulcer repair with increasing days after exposure to ketorolac in group 3 and group 4, but in group 2 there was tissue damage that continued with increasing examination days.

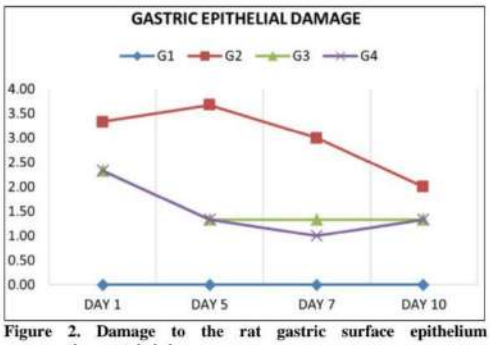

Figure 2. Damage to the rat gastric surface epithelium representing gastric injury.
Epithelial defect scores on group 2 (G2) were seen to be highest on day 5 after exposure to ketorolac. Epithelial defect scores showed the lowest values on day 5in both groups 3 (G3) and 4 (G4), group 4 (G4) showed the lowest values for epithelial defects on day 7.

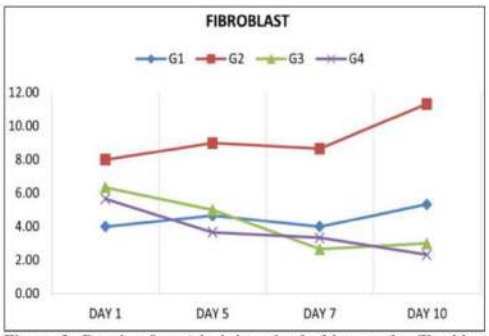

Figure 3. Repair of gastric injury by looking at the fibroblast expression score.
From the results of the study, it can be seen that the expression of fibroblasts as an expression of tissue damage was seen to have the highest value in each group on day 1. In groups 3 and 4 (G3 and G4), fibroblast expression began to decrease, indicating gastric ulcer repair on day 5, and fibroblast expression decreased on day 7 to day 10. However, the expression value of fibroblasts increased every day in group 2 (G2). This showed an increase in gastric injury repair with increasing days after exposure to ketorolac in group 3 (G3) and group 4 (G4), but in group 2 (G2) there was tissue damage that continued with increasing examination days.

DISCUSSION:

Effects of *Lactobacillus plantarum* IS-10506 on Repair Acceleration Ketorolac-induced Gastric Injury by Observing the Repair of Gastric Mucosal Epithelial Damage The results of the study were based on microscopic parameters with assessing epithelial damage (gastric injury) shows if: On the first day after exposure to ketorolac, gastric epithelial damage occurred in all treatment groups (group 2, group 3, group 4), the highest value of epithelial damage occurred in group 2, while the value of epithelial damage in group 3 and group 4 was lower compared to group 2.The healing of gastric injury began withdecreased damage score in group 3 and group 4 on the 5th day after exposure to ketorolac. Meanwhile, in group 2, the value of epithelialdamage was increasing on the 5th day. Improvement of gastric injury in the group that was given probiotics was seen to occur on the 5th day and continued until the 7th day.Groups 3 and 4 showed the same healing gastric injury score on the 10th day after exposure to ketorolac.From the results of the microscopic examination, it can be concluded that:ketorolac at a dose of 30mg/kg body weight can cause gastric injury in rats after 1 day of administration.Healing of gastric injury in the group given *Lactobacillus plantarum* IS-10506 before exposure to ketorolac occurred on day 5 after exposure to ketorolac (group 3) and the same thing occurred in group 4 (the group that received *Lactobacillusplantarum* IS-10506 as preventive and as curative), where the gastric injury healing process occurred on the 5th day after exposure to ketorolac.The administration of *Lactobacillusplantarum* IS-10506 could accelerate the repair of gastric injury after induction of ketorolac in group 3 and group 4 rats when compared to the group that did not receive *Lactobacillusplantarum* IS-10506 (group 2).

This study assessed the improvement of gastric injury induced by ketorolac administration in Wistar rats by taking 2 parameters, repair of epithelial defectsand fibroblast cells. Use of non-steroidal anti-inflammatory drugs for a prolonged period of time can result in some gastrointestinal damage (NSAIDs).[14–16]Gastric injury induction in this study using ketorolac at a dose of 30 mg/kg body weight, can significantly inhibit COX-1 and COX-2 activity by 91% so that it can cause significant gastric damage in patients with gastric injury.[17] Gastric injuriesare induced by ketorolac through cyclooxygenase inhibition processes and partly by cyclooxygenase independent mechanisms, which are mostly caused by local processes.[18] By using a variety of processes, increased mucus production by the gastric mucosal cells can stop gastrointestinal injury.[19] Maintenance of mucosal blood flow during epithelial damage is very important in the process of repairing

damaged tissue, before progressing deeper into the submucosal layer.[20] Damage to the gastric mucosal epithelium due to oral administration of NSAIDs involves several mechanisms. The gastroprotective prostaglandins E1(PGE2) and prostaglandin (PGI2), which are mostly generated by COX-1, are synthesized less, which contributes to the gastro-intestinal (GI) adverse effects of NSAIDs.[21,22] Acidic NSAIDs can directly damage epithelial cells. Several cytotoxic mechanisms, namely the induction of osmotic lysis that occurs after NSAIDs interact with epithelial cells, then epithelial cell death occurs after the release of oxidative phosphorylation. Nonsteroidal anti-inflammatory drugs (NSAIDs) can also reduce mucus and bicarbonate secretion, thereby decreasing the effectiveness of the juxta-mucosal pH gradient in protecting the epithelium. Nonsteroidal anti-inflammatory drugs (NSAIDs) can also interfere with the active phospholipid layer on the mucosal surface. This will make the mucosa less able to withstand the damage caused by luminal acid.[23] Healing of gastric injury is a complex process, initial healing by rapid migration of epithelial cells and inflammatory cells that appear in the early phase of healing are replaced by fibroblasts, while in the late healing phase they are replaced by microvasculature.[24]

Previous experimental studieshave proven the ability of certain probiotic strains to accelerate the healing of the gastric injury.[25] Research conducted by Murali et al in 2010 showed that live probiotic strains induce the production of protective cytokines that increase epithelial cell regeneration and inhibit epithelial cell apoptosis.[26] The results of research conducted by Yan and Polk in 2002 showed that Lactobacillus rhamnosus GG could prevent apoptosis of intestinal epithelial cells.[27] Research conducted by Neish et al in 2000 showed that probiotic bacteria in rat or human colon cell culture can activate anti-apoptotic Akt/protein kinase B and inhibit the activation of p38-activated protein kinase/proapoptotic mitogen by tumour necrosis factor(TNF), IL-1., or interferon (IFN).[28]

Research conducted by Halperet al in 2003, Resta-Lenert and Barrett in 2003, and Valdez in 2005found that probiotic metabolites have been reported to induce angiogenesis, proteoglycan deposition, and wound healing.[29–31] Research conducted by Halper et al in 2003 found that metabolite products from lactobacilli cultures can induce angiogenesis and proteoglycan deposition which are very important in remodelling tissue damage.[31] The polysaccharide fraction isolated from the cell walls of bifidobacteria, lactobacilli, and streptococci was reported to have an anti-ulcer effect and the polysaccharide fraction from Bifidobacterium bifidum YIT4007 was found to up-regulate epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF). These findings prove that probiotics can help heal mucosal ulcers. Yoghurt containing *Lactobacillus gasseri* OLL2716 (LG21 yoghurt) showed a gastroprotective effect against HCl-induced gastric mucosal damage and antral ulcers in the stomach of rats compared to unfermented milk. The protective effect is the ability of probiotics to increase PGE2 production and increase gastric mucosal blood flow, fiber increases bicarbonate secretion.[28]

Research conducted by Ogueke et al in 2010 found that probiotic strains can stimulate and modulate the immune system.[32] Research Pathmakanthan et al 2004 showed that the administration of *Lactobacillus plantarum* can increase the synthesis and secretion of IL-10 in macrophages originating from the inflamed colon.[33] Research conducted by Ng et al in 2009 showed that probiotics can affect lymphocytes through changes in stimulation caused by changes in antigen-presenting cells (APCs), macrophages, platelet derived growth factor (PDGF), EGF, fibroblast growth factor (FGF), and cytokines.[34] Another experimental study showed that probiotics may contribute to the prevention and modality of gastric ulcer therapy by increasing: i) production of prostaglandins, mucins, growth factors and anti-inflammatory cytokines, ii) ratio of cellular proliferation to apoptosis, iii) gastric mucosal integrity, iv) trans-resistance mucosa and v) angiogenesis.[9]

Probiotics have been extensively studied in animal models and beneficial effects of several species and strains have been demonstrated on immunological, metabolic, and neuroendocrine dysfunction. Probiotics engage with the mucosal immune system via Toll-like receptors to promote type 1 helper T cell differentiation. As a consequence, antibody production is increased, phagocytic and natural killer cell activity is increased, and activation of the NFκ-B inhibitory pathway is increased. This results in the induction of T cell apoptosis, upregulation of anti-inflammatory cytokines, such as interleukin (IL)-10, and transformation of growth factors and downregulation of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interferon-gamma, and IL-8.[35] Uchida et al. found that Lactobacillus can inhibit ileal ulcers in mice by suppressing the growth of ulcer-inducing bacteria.[25]

Effects of *Lactobacillus plantarum* IS-10506 on Repair Acceleration Ketorolac-induced Gastric Injury by Observing the Fibroblast Cell:

This study showed that fibroblast expression as an expression of tissue damage showed a high value in each group on day 1. Fibroblast expression began to decrease on day 5, followed by a decrease in fibroblast expression on day 7 to day 10 ingroup 3 and group 4. Based on statistical tests showed if the expression of fibroblasts in

the given group *Lactobacillus plantarum*IS-10506 there was a decrease in fibroblast expression on day 5, where the decrease in fibroblast expression did not differ between day 1 and day 5. This indicated that repair of gastric injury increased with days after exposure to ketorolac in group 3 and group 4. Group 2 showed an increased expression of fibroblasts every day of necropsy. This shows that the group that received *Lactobacillus plantarum* IS-10506 as preventive and curative showed increased fibroblast expression on day 1, and decreased on day 5 onwards, indicating an accelerated repair of gastric ulcers after day 1 exposure to ketorolac.

Fibroblasts are cells that are normally found in the gastric mucosa, which function to upgrade the damage if an ulcer occurs in the gastric mucosa through granulation tissue. Fibroblasts are the forerunner of microvascular and connective tissue both in vivo and in vitro that play a role in the wound healing process.[28] Research conducted by Nasrabadi et al. in 2011 stated that in a gastric ulcer model performed on rats, fibroblast expression showed the highest value on days 3 and 5 with the administration of probiotics (Lactobacillus plantarum) compared to controls, which showed fibroblast expression on healingulcer on the 7th day.[36] The migration process from fibroblasts to granulation tissue is triggered by several growth factors, namely: transforming growth factor (TGF), platelet derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF) and several cytokines. This study showed that *L. plantarum* could increase the expression of several growth factors in the expression of fibroblasts in the healing process of gastric ulcers. Research conducted by Nasrabadi et al in 2011 showed that neutrophils, macrophages, and fibroblasts were significantly reduced on the seventh and fourteenth days after ulcer induction in the experimental group compared to the control and negative control groups. These data indicate that inflammation has decreased.[36]

Research conducted by Playford and Wright has analyzed the sequential expression of various genes during gastric ulcer healing.[37] Based on the analysis differentiated genes involved in the early response, EGF-R, c-fos, c-jun, EGR-1, Sp-1, and trefoil factor family/Spasmolytic polypeptide (TFF-2/SP), all of which were activated immediately after ulcer formation (within 30 minutes); intermediate response genes, EGF, bFGF, PDGF, and VEGF (activated within 6 hours-2 days); and the slow response genes, hepatocyte growth factor (HGF), intestinal trefoil factor (ITF), and c-met/HGF-R (activated within 14 days). Several growth factors are produced by epithelial cells, for example,trefoil family factor (TFF), EGF, and TGFα; and others, for example, PDGF, vascular endothelial growth factor (VEGF), HGF, and basic fibroblast growth factor (bFGF), by mesenchymal cells. Upregulation of TFF may precede upregulation of other growth factors, such as EGF and TGF, indicating that TFF peptides have the potential to initiate gastric ulcer healing.[4]

Nagaoka et al reported that the polysaccharides Bifidobacterium breve YIT4014 and 4043I and Bifidobacterium bifidum YIT4007 were able to repair and protect the rat mucosa from erosion and gastric ulcers induced by acetic acid and ethanol. Polysaccharides from this probiotic mixture were found to increase the expression of growth factors such as fibroblast growth factor and epidermal growth factor in addition to 6-ketoprostaglandin F1.[38]

CONCLUSION:

This study demonstrated that orally administered ketorolac30 mg/kg body weight induced gastric mucosal injury in the rat. The administration of probiotics (L.*plantarum* IS-10506) can accelerate the healing process of gastric injury by enhancing the expression of gastric mucosal epithelial repair and decreasingthe inflammation process seen by fibroblast cell expression.

CONFLICT OF INTEREST:

The authors declare no conflict of interest

ACKNOWLEDGEMENT:

We wish to thank our staff in the Pediatric Ward, the doctors, nurses, and the administrator for granting us permission and necessary support to conduct our research.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7