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Effect of Probiotic on the improvement of Ibuprofen-induced Gastric Mucosal Injury Model in Wistar Rats

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ABSTRACT

Introduction: Gastric mucosal injury is a situation that is often obtained as a result of various conditions in humans, both adults and children. Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to cause gastric mucosal injury as a side effect. Ibuprofen is the most commonly used and most frequently prescribed NSAID. In this study, the probiotic used is from the lactobacillus strain called Lactobacillus Plantarum IS-10506. The aim of this study is to determine the effect of probiotic on repairing the ibuprofen-induced gastric mucosal injury. **Methods:** Thirty-two Wistar rats were divided into 2 groups: Ibuprofen group (K1), which received Ibuprofen then the second group (K2) which received probiotics LIS-10506 for 7 days after being given Ibuprofen. Necropsy was done on days 1, 3, 5 and 7 with gastric as unit analysis. The microscopic examination was conducted to evaluate the structure of gastric mucosal measured based on the Histology Activity Index (HAI) by Rogers (2012). The statistical analysis used Kruskal Wallis, Mann-Whitney test, $p < 0.05$ was considered statistically significant. **Results:** None of the research subjects had dropped out of the test during the observation period. The epithelial damage in between groups K1 and K2 there was no significant difference on the first day ($p=0.456$), third ($p=0.456$), fifth ($p=0.099$), but on the seventh day there was a significant difference ($p=0.034$). **Conclusion:** Probiotic LIS-10506 has an effect on the repair of gastric mucosal damage induced by ibuprofen.

Keywords: probiotic; ibuprofen; gastric mucosal injury

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (IBP) are known to cause gastric mucosal injury as a side effect. Ibuprofen is the most commonly used and most frequently prescribed NSAID [1,2]. It is a non-selective inhibitor of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) [3]. Although its anti-inflammatory properties may be weaker than those of some other NSAIDs, it has a prominent analgesic and antipyretic role. Its effects are due to the inhibitory actions on cyclo-oxygenases, which are involved in the synthesis of prostaglandins. Prostaglandins have an important role in the production of pain, inflammation and fever [4].

One of the important factors in gastric injury induced by NSAIDs is an endogenous prostaglandin (PG) deficiency caused by the inhibition of COX-1 and COX-2. PGs protect the gastric mucosa against necrosis induced by NSAIDs or ethanol [5,6]. COX-1 is constitutively expressed in various tissues, including the stomach, as a housekeeping protein, whereas COX-2 is expressed in response to cytokines in most tissues under pathologic conditions such as inflammation [7]. Studies using selective COX-1 or COX-2 inhibitors have indicated that the gastric ulcerogenic properties of NSAIDs are caused by inhibition of both COX-1 and COX-2 [8,9]. However, several reports suggest that other elements such as free radicals, disturbances of microcirculation, and hypermotility may be involved in the pathogenic mechanisms [5,10,11]. Furthermore, it has been reported that other risk factors, including diabetes

and concomitant use of other agents, aggravate gastric lesions induced by NSAIDs [12,13,14]. Taken together, although PG deficiencies due to inhibition of COX-1 and COX-2 play an important role in gastric side effects, the mechanisms by which NSAIDs induce gastric injury remain elusive. Our present study examined the effect of probiotic on repairing the ibuprofen-induced gastric mucosal injury.

MATERIAL AND METHODS

Samples

This study received ethical approval from the Animal Care and Use Committee (ACUC) of the Veterinary Medicine School, Universitas Airlangga (Indonesia). Male Wistar rats ($n = 32$, 12 weeks old, approximately 150-200 g were obtained from LPPT UGM). The rats were fed standard laboratory chow and tap water ad libitum. Rats were routinely monitored for body weight (BW). The rats were deprived of food, but not water, for 18-20 hours before an experiment.

Selection of Doses of test Drugs

After 7 days of acclimatization, thirty-two rats were equally assigned into 2 groups. The first group (K1) was induced with IBP (No. Reg GTL9907111310A1 PT First Medipharma Indonesia) 300 mg/kg suspended in sterile water through gavage on the first day, then treated with distilled water daily on the following days. The second group (K2) received probiotics LIS-10506 for 7 days after being given Ibuprofen.

The probiotic *Lactobacillus Plantarum* IS-10506 at a dose of 2.86×10^{10} CFU/g was administered individually every day to the K2 group for 7 days. Each group was further divided into 4 groups whose members have sacrificed as many as 4 rats on days 1, 3, 5, and 7, then gastric tissue was collected.

Measurement of epithelial defects

The stomachs were removed, inflated by injecting 10 ml of saline, immersed in 1% formalin for 1 hour to fix the gastric tissue, and opened along the greater curvature. The stomach was removed and scored for epithelial defects based on the Histology Activity Index (HAI) according to Rogers (2012) modified by assessing epithelial damage, these criteria have a score range of 0-4 (0 = no abnormalities, 1 = abnormalities <25% of the entire field of view, 2 = abnormalities of 25%-50% of the entire field of view, 3 = abnormalities 50% - 75% of the entire field of view, 4 = abnormalities > 75% of the entire field of view). The assessment was carried out based on observations from the entire gastric field of view with a magnification of 100x - 400x [15].

Histology

The gastric mucosa was examined with a microscope after the drugs administration. The animals were euthanized on

days 1, 3, 5, and 7 after the drug administration under ketamine anesthesia, and the stomachs were excised, immersed in 10% neutralized formalin, and embedded in paraffin. The sections (8 mm) were cut using a microtome and stained with hematoxylin and eosin.

Statistical Analysis

Gastric injury data results are presented as mean \pm SD per group. Statistical analyses with Kruskal-Wallis and Mann-Whitney U test, with $p < 0.05$ was considered statistically significant.

RESULTS

In this study, to investigate the effect of probiotic on repairing the ibuprofen-induced gastric mucosal injury model, epithelial defects were measured based on The Histology Activity Index (HAI) according to Rogers (2012) modified. Through random allocation into 2 treatment groups and screening before treatment with inclusion criteria, namely the age of the rats at 12 weeks and male sex with a bodyweight of 150-200 grams. The description of epithelial damage to the gastric mucosa after treatment between the ibuprofen group (K1) and the ibuprofen-probiotic group (K2) in *Wistar* rats necropsied on days 1, 3, 5, and 7 is shown in table 1.

TABLE 1: Comparison of epithelial damage between the ibuprofen group (K1) and the ibuprofen-probiotic group (K2)

Parameter	Observation	K1	K2	p
		Mean (SD)	Mean (SD)	
Epithelial damage	Day - 1	3.67 (0.58) ^a	3.33 (0.58) ^a	0.456
	Day - 3	3.67 (0.58) ^a	3.33 (0.58) ^a	0.456
	Day - 5	3.33 (0.58) ^a	2.33 (0.58) ^{ab}	0.099
	Day - 7	3.00 (0.00) ^a	1.33 (0.58) ^b	0.034*
	p	0.216	0.045*	

Description: *Mean difference is significant at p-value <0.05
^{ab} superscript: the same shows no difference between groups

In table 1 it can be seen that the epithelial damage in the ibuprofen group (K1) was compared with the ibuprofen-probiotic group (K2) on the first, third, fifth day and there was no significant difference, while on the seventh day there was a significant difference (p=0.034). In the ibuprofen group (K1) there was no significant difference in epithelial damage on the first, third, fifth, and seventh days (p=0.216) with the mean epithelial damage on K2 decreased on the seventh day,

While in K2 there was a significant difference (p=0.045) in epithelial damage, namely on the first and seventh day and the third and seventh day with the mean epithelial damage decreasing until the seventh day and significantly different when compared to the ibuprofen group (K1) on the seventh day of observation. These results indicate that the probiotic *Lactobacillus Plantarum* IS-10506 has an effect on the repair of ibuprofen-induced gastric mucosal epithelial damage on the seventh day.

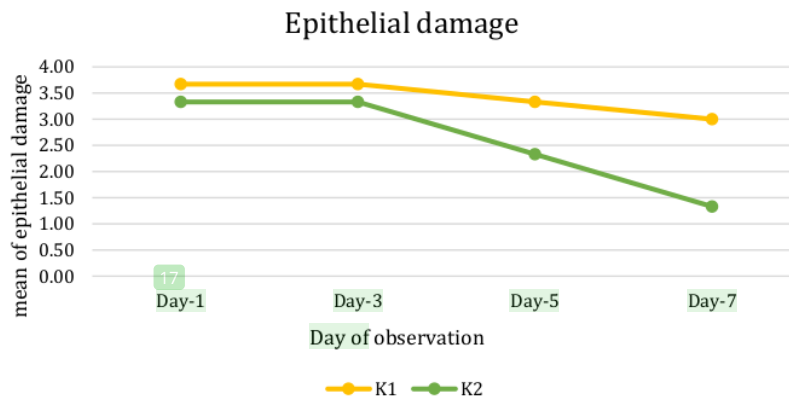


FIGURE 1: Comparison of epithelial damage in gastric mucosa between the ibuprofen group (K1) and the ibuprofen-probiotic group (K2)

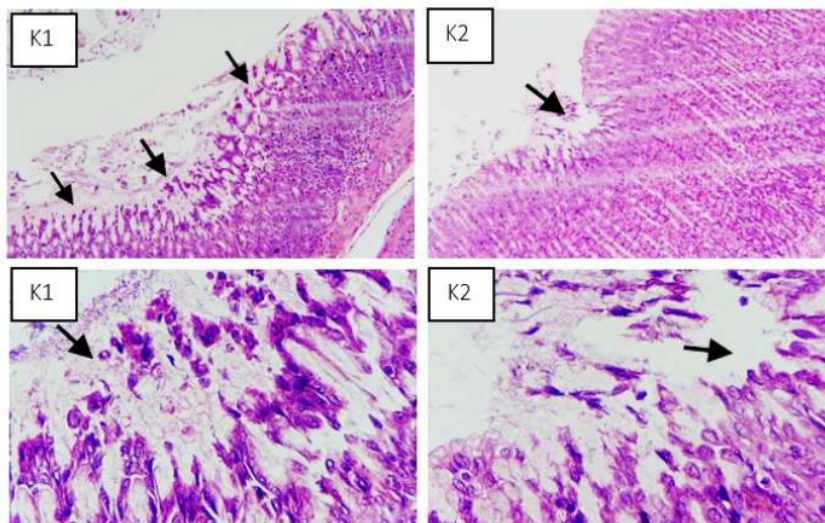


FIGURE 2: A comparison of epithelial damage between groups on the fifth day, (↗) shows gastric mucosal epithelial damage with H&E staining, magnification 100x (top image), and 400x (bottom image). K1 (ibuprofen group), K2 (ibuprofen-probiotic group).

DISCUSSION

This study investigates the effect of probiotic on repairing the ibuprofen-induced gastric mucosal injury model. The first group (K1) was induced with IBP 300 mg/kg suspended in sterile water through gavage on the first day, then treated with distilled water daily on the following days. The second group (K2) received probiotics LIS-10506 for 7 days after being given Ibuprofen.

Ibuprofen group (K1) and the ibuprofen-probiotic group (K2), there were no significant differences on the first, third, and fifth day, while on the seventh day there was a significant difference. Based on the day of observation, on K2 epithelial damage, there were significant differences, namely on the first and seventh days and third and seventh days with the mean epithelial damage decreasing until the seventh day and significantly different when compared to the ibuprofen group (K1) on the seventh day of observation. These results indicate that there is an effect of probiotic *Lactobacillus Plantarum* IS-10506 on the acceleration of repair of gastric mucosal epithelial damage induced by ibuprofen.

Gastric mucosa damage is a situation that often occurs as a result of various conditions in humans, both adults, and children [16]. The mechanism of damage to the gastric mucosa has been widely described in various studies over the last few decades. Although the mechanism of injury to the gastric mucosa can be different, the consequences caused by the injury are the same, namely erosion of the gastric mucosa. Erosion of the gastric mucosa can also develop into ulcers which can be chronic [17].

NSAIDs are known to cause tissue damage such as gastrointestinal damage, nephrotoxicity, and hepatotoxicity. There is evidence that oxidative stress is involved in this toxicity [18]. The mechanism by which NSAIDs cause damage to the gastric mucosa is mainly due to the inhibition of the cyclooxygenase (COX) enzyme and the suppressive effect of prostaglandins on the mucosal barrier [19]. It has been suggested that neutrophils and oxygen radicals dependent on microvascular injury may have an important role in causing mucosal damage in response to NSAID administration (aspirin, ibuprofen, diclofenac, indomethacin, and piroxicam [20].

In addition to the gastric mucosal defense barrier factor, the antioxidant system is also an important factor that protects the structure and function of the gastric mucosa [21]. In a healthy body condition, the balance of reactive oxygen species (ROS) is maintained through nuclear factor erythroid-2 related factor 2 (Nrf2) [22,23]. When stimulated by external factors (NSAIDs, alcohol, cigarette smoke, etc.) excessive ROS production and decreased antioxidant activity (superoxide dismutase (SOD), catalase (CAT), glutathione (GSH)) cause an imbalance in the antioxidant system [24,25]. The imbalance of the antioxidant system can cause chemical damage to the gastric mucosa, such as lipid peroxidation in cell membranes, and ultimately produce gastric damage [26].

A number of studies have shown that probiotics can be used for the treatment of gastric ulcers, especially the administration of the probiotic strain *Lactobacillus* accelerates ulcer healing [17]. The beneficial effects of probiotics depend primarily on their ability to withstand acidic conditions and hydrolytic enzymes and bile content in the stomach and duodenum. Several studies have shown that the degree of acidity, duration of exposure and strain of probiotics are the main factors affecting their survival. Among probiotic strains, lactic acid bacteria such as *Lactobacillus* and *Bifidobacterium* show remarkable ability to survive gastric transit and, therefore, are widely used in many pharmaceutical and dairy probiotic products [17,27].

Probiotics are not only effective against gastric ulcers caused by acetic acid, ethanol, or stress but also play an important role in the prevention or treatment of NSAID-induced ulcers. Senol et al (2011) on aspirin-induced gastric mucosal damage showed that probiotics could inhibit mucosal lipid peroxidation, stimulate sIgA secretion and stabilize mast cell degradation in gastric mucosa [28]. A study conducted by Konturek et al (2009) showed that probiotics can repair gastric mucosal lesions with anti-inflammatory action, induce ghrelin and HSP70 synthesis, increase gastric microcirculation, and increase prostaglandins, nitric oxide, and neuropeptides [29].

A study by Lam et al (2007) on gastric mucosal damage induced by acetic acid showed that the probiotic *Lactobacillus rhamnosus* GG could inhibit cell apoptosis and induce angiogenesis. *L. rhamnosus* GG colonizes the edges of gastric mucosal ulcers. The ratio of apoptosis to cell proliferation was markedly decreased and accompanied by a significant upregulation of the expression of ornithine decarboxylase (ODC) and B-cell lymphoma2 (Bcl-2) proteins at the ulcer margins. Angiogenesis was also significantly stimulated along with the induction of vascular endothelial growth factor (VEGF) expression. *L. rhamnosus* GG also increases the phosphorylation of the epidermal growth factor receptor (EGF receptor) without changing the expression of the total EGF receptor [30].

Another study showed the use of multi-strain probiotics (*Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Propionibacterium* and *Acetobacter*) improved ulcer healing by restoring the balance between pro and anti-oxidants in the gastric mucosa. In addition, multi-strain probiotics (consisting of *Bifidobacterium animalis* VKL and VKB with or without *Lactobacillus casei* IMVB-7280) increased the recovery of stress hormones (adrenocorticotropin and corticosterone), decreased proinflammatory cytokines and increased anti-inflammatory cytokines [17,27]. Research conducted by Ayyanna et al (2018) showed that probiotic strains (*Lactobacillus mucosae* AN1 and *Lactobacillus fermentum* SNR1) administered to experimental mice significantly reduced inflammatory edema. In the group given probiotics found effective anti-inflammatory properties. On immunohistochemical examination, it was found that the expression of the anti-inflammatory cytokine IL-10 was higher than the proinflammatory cytokine IL-6. qRT-PCR and ELISA results showed that there was upregulation of anti-inflammatory cytokines and downregulation of proinflammatory cytokines. Therefore, the antioxidant mechanism of probiotics given to Wistar rats may be by inhibiting the synthesis of prostaglandins due to the high expression of anti-inflammatory cytokines.

CONCLUSIONS

From this study, it can be concluded that probiotic *Lactobacillus plantarum* IS-10506 has an effect on the repair of gastric mucosal damage induced by ibuprofen.

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