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Original Article

Effects of *Aloe Vera* Extract on Basal Cell Thickness and Lymphocyte Infiltration at the Gastroesophageal Junction in a Rat Model of Gastroesophageal Reflux Disease

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Abstract

Background: Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder with increasing global prevalence. *Aloe vera* contains bioactive compounds with potential anti-inflammatory properties. This study aimed to evaluate the anti-inflammatory effects of Aloe vera extract in a Sprague-Dawley rat model of GERD.

Methods: This experimental study included 32 male Sprague-Dawley rats randomly divided into eight groups: normal (N), negative control (NC), two positive controls receiving pantoprazole for 7 or 14 days (PCI and PCII), and four treatment groups receiving *Aloe vera* extract at doses of 250 or 500 mg/kg body weight for 7 or 14 days (DI–DIV). After treatment, the rats were euthanized and gastroesophageal junction (GEJ) tissues were collected for histopathological analysis. Basal cell thickness and lymphocyte infiltration were assessed. Data were analyzed using one-way ANOVA followed by post hoc testing.

Results: Administration of *Aloe vera* extract at doses of 250 and 500 mg/kg body weight significantly reduced basal cell thickness compared with the untreated GERD group ($p<0.05$). However, no significant reduction in lymphocyte infiltration was observed ($p>0.05$).

Conclusions: *Aloe vera* extract exhibits anti-inflammatory effects in GERD-induced rats by reducing basal cell thickness at the GEJ. These findings suggest its potential as a complementary therapeutic approach for GERD, although further studies are needed to evaluate long-term efficacy and safety.

Keywords: *Aloe vera* extract, basal cells thickness, gastroesophageal junction, gastroesophageal reflux disease, lymphocyte infiltration.

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Introduction

Sleep is a fundamental humans' need.[1] Gastroesophageal reflux disease (GERD) is a chronic digestive disease, defined by regurgitation of gastric contents into the esophagus. GERD has a fairly high prevalence rate in the world. In Indonesia, the prevalence of GERD is recorded at 4.9% of the total population.[1] Interestingly, the prevalence of GERD in 2016 has reached 27.4% among Indonesian medical doctors.[1]

Clinically, GERD often appears with symptoms of heartburn due to gastric contents regurgitation. However, atypical symptoms may occur, including nausea and bloating,as well as extraesophageal manifestations such as dental erosion, chronic cough, sore throat, and even asthma.[2] Recurrent esophageal reflux might eventually cause several

changes in histological characteristics. The ability of squamous epithelium to repair is reduced and abnormal differentiation occurs in the esophageal epithelium, leading to metaplasia.[3,4] The changes in squamous epithelial proliferation are designated as basal cell hyperplasia and infiltration of inflammatory cells such as lymphocytes.[5] Basal cell hyperplasia representsa proliferative response to acid reflux and pepsin-induced damage to tight junctions and adherens complexes between esophageal squamous cells. This disruption permits hydrogen ions to penetrate the epithelium, resulting in cellular injury at the luminal surface.[6–8]

Aloe vera is a commodity that is in demand because of its beneficial compounds. The content in *Aloe vera* is amino acids, saccharides, minerals, vitamins, anthraquinones, salicylic acid, enzymes, lignin, and saponins.[9] It also contains polysaccharides, such as glucomannan, mannan (acetate), and pectin. Polysaccharides have antioxidant- and immunostimulant effects by increasing the production of Nitric Oxide (NO) and IL-6 in macrophage function.[10] *Aloe vera* has been proven to be effective as an alternative medicine for several diseases. This study aimed to explore the anti-inflammatory effects of *Aloe vera* extract on the histopathological features of GERD model rats.

Methods

This study employed a quasi-experimental This experimental study was conducted from June to August 2024 in the Animal and Biochemistry Laboratory, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia. Ethical approval was obtained from the Ethics Committee of the Atma Jaya Indonesian Catholic University with approval number No. 05/01/KEP-FKIKUAJ/2024.

Aloe vera leaves were washed and weighed as much as 250 grams, then the simplicia were smoothen using an electric blender. The *Aloe vera* were extracted thoroughly with 70% alcohol with a ratio of 1:2 in an Erlenmeyer flask for 24 hours (Figure 1). The extract was filtered and evaporated in an oven at 60°C to obtain a concentrated extract.

Thirty two Sprague-Dawley rats were randomly divided into eight groups: normal (N), negative control (NC), positive control I (PCI), positive control II (PCII), and four treatment groups (DI, DII, DIII, and DIV). The normal group was only given rat feed, whereas the NC group was induced to be in GERD condition.

In brief, GERD induction was carried out by inserting 10 mM ascorbic acid together with 1 mL of HCl pH 2.0 through a 3.5 mL F.R Feeding tube to the lower part of the rat's stomach, at a rate of 0.5 mL per 30 minutes. The rats were also given 1.5 mL of Sodium nitrite (NaNO3) and 1 mL of Sodium thiocyanate (NaSCN) using a probe (Figure 2).

The PCI and PCII were given Proton Pump Inhibitor (PPI) treatment, which was pantoprazole 30 mg for 7 days and 14 days, respectively.The DI and DII groups received *Aloe vera* extract at doses of 250 and 500 mg/kgBW, respectively, for 7 consecutive days, and DIII and DIV groups received *Aloe vera* extract at doses of 250 and 500 mg/kgBW, respectively, for 14 consecutive days. After 7 or 14 days, for DI and DII or DIII and DIV respectively, the rats were terminated and the gastroesophageal junction (GEJ) was taken and histopathological tissue were examined to assess the ratio of basal cell thickness and lymphocyte count (Figure 3).

The results of basal cell thickness were categorized into 3 groups; the normal group (<15% of total epithelium), mild-moderate (15–30%) and severe (>30%).[11] The number of lymphocytes was classified into normal (0–9 cells), mild-moderate (10–30 cells), and severe (>30 cells).[12] The histopathological tissue was stained with Hematoxylin-Eosin (HE) staining and assessed under a light microscope with a magnification of 40x.

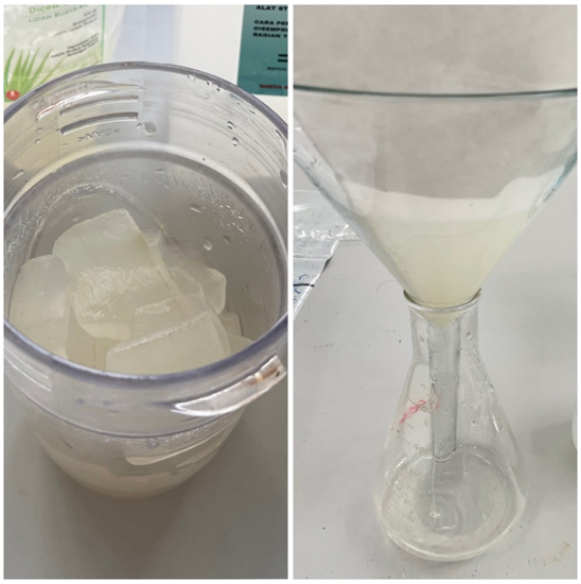

Figure 1 *Aloe Vera* Extract Used in the Study

Figure 2 Induction of Gastroesophageal Reflux Disease (GERD) in Sprague-Dawley Rats (Left) and Administration of *Aloe Vera* Extract (right)

Data was analyzed using SPSS version 23.0 through ANOVA test to determine differences in values between groups regarding basal cell thickness and number of lymphocytes and Tukey's post hoc analysis to determine groups that had significant differences in decreasing basal cell thickness and number of lymphocytes.

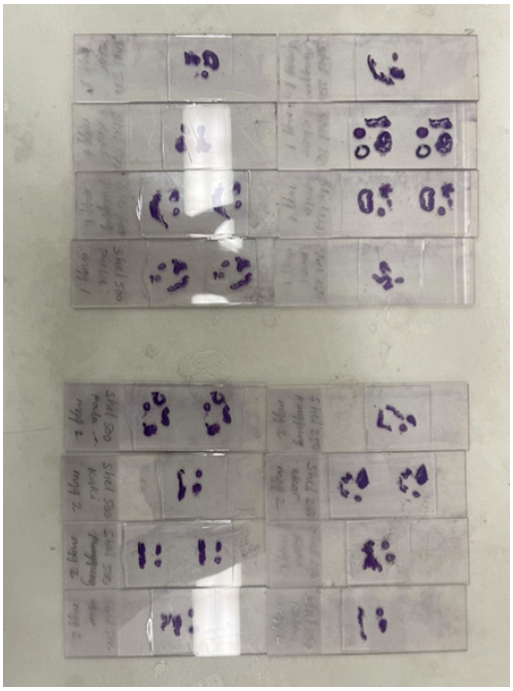

Figure 3 Histopathological Appearance of the Gastroesophageal Junction in Sprague-Dawley Rats Across Experimental Group

Table 1 Basal Cell Ratio and Lymphocyte Counts Among Experimental Groups in a GERD Rat Model

Parameter	N	NC	PI	PII	DI	DII	DIII	DIV	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Basal cell ratio	10.64 ± 1.05	21.72 ± 7.06	10.10 ± 1.72	7.55 ± 1.29	12.00 ± 3.87	14.55 ± 4.05	10.83 ± 1.57	10.24 ± 1.45	0.001*
Lymphocytes	0.25 ± 0.25	0.35 ± 0.34	0.73 ± 0.30	0.00 ± 0.00	0.40 ± 0.36	0.60 ± 0.69	0.20 ± 0.16	0.20 ± 0.23	0.240

Note: *p<0,05; SD=Standard deviation, N=Normal, NC=Control Negative, PI= Pantoprazole 30 mg 7 days, PII=Pantoprazole 30 mg 14 days, DI= Aloe vera 250 mg/kgBB 7 days, DII= Aloe vera 500 mg/kgBB 7 days, DIII= Aloe vera 250 mg/kgBB 14 days, DIV= Aloe vera 500 mg/kgBB 14 days

Results

The results showed that the basal cell ratio in the positive control group had the highest percentage (21.72±7.06%), while the group treated with PPI for 14 days had the lowest percentage (7.55±1.29%).

Regarding the lymphocyte count, the pantoprazole 7-day group had the highest mean value (0.73±0.30), whereas no lymphocyte cells were observed in the histological sections of the group treated with PPI for 14 days (Table 1). The results also show that the basal cell ratio variable had a statistically significant difference with a p-value of 0.001, whereas the lymphocyte count variable had a p-value of 0.24, indicating no significant difference. These findings suggest that only the basal cell ratio showed a significant effect across treatment groups.

Post hoc LSD analysis revealed a significantly higher basal cell ratio in the positive control

Table 2 Post Hoc Comparison of Basal Cell Ratio Between Experimental Groups

Comparison	Mean Difference in Basal Cell Thickness	95% CI		p
		Lower Limit	Upper Limit	
N and NC	-11.07	-16.21	-5.93	0.000*
N and PI	0.54	-5.01	6.09	0.842
N and PII	3.09	-2.46	8.64	0.261
N and DI	-1.35	-6.49	3.78	0.590
N and DII	-3.90	-9.04	1.23	0.129
N and DIIII	-0.182	-5.32	4.95	0.942
N and DIV	0.41	-4.73	5.54	0.872
NC and PI	11.61	6.05	17.16	0.000*
NC and PII	14.16	8.61	19.71	0.000*
NC and DI	9.71	4.57	14.85	0.001*
NC and PII	7.16	2.02	12.30	0.008*
NC and PIII	10.89	5.74	16.03	0.000*
NC and PIV	11.47	6.33	16.61	0.000*
PI and PII	2.55	-3.38	8.48	0.383
PI and DI	-1.89	-7.44	3.65	0.486
PI and DII	-4.44	-10.00	1.10	0.111
PI and DIII	-0.72	-6.27	4.83	0.790
PI and DIV	-0.13	-5.68	5.41	0.960
PII and DI	-4.44	-9.99	1.10	0.111
PII and DII	-6.99	-12.55	-1.44	0.016*
PII and DIII	-3.27	-8.82	2.28	0.235
PII and DIV	-2.68	-8.23	2.86	0.327
DI and DII	-2.55	-7.69	2.58	0.314
DI and DIII	1.17	-3.96	6.31	0.641
DI and DIV	1.76	-3.38	6.90	0.485
DII and DIII	3.72	-1.41	8.86	0.147
DII and DIV	4.31	-0.82	9.45	0,096
DIII and DIV	-0.58	-5.72	4.55	0.815

Note:*p<0.05; N=Normal, NC=Control Negative, PI= Pantoprazole 30 mg 7 days, PII=Pantoprazole 30 mg 14 days, DI= Aloe vera 250 mg/kgBB 7 days, DII= Aloe vera 500 mg/kgBB 7 days, DIII= Aloe vera 250 mg/kgBB 14 days, DIV= Aloe vera 500 mg/kgBB 14 days

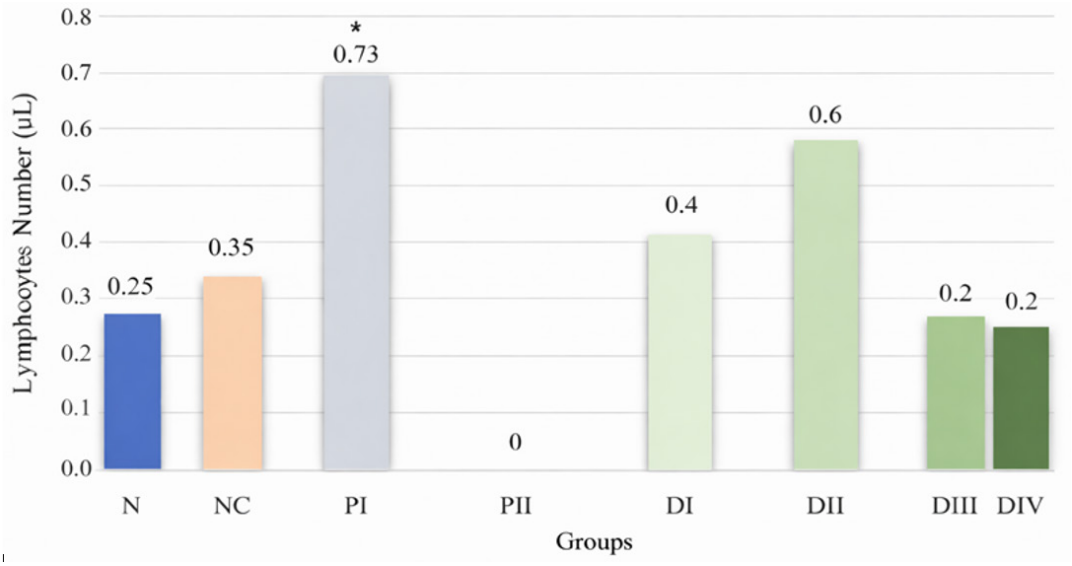

Figure 4 Comparison of Lymphocyte Counts Among Experimental Groups

compared to the negative control (p=0.000) and all treatment groups (p<0.05). The 14-day PPI group (PII) differed significantly from the 7-day aloe 500 group (DII) (p=0.016), with a higher basal cell ratio observed in the latter. However, no significant differences were found among the remaining treatment groups, indicating similar efficacy in reducing basal cell ratio.

The lymphocyte counts between groups showed no significant difference, (p=0.24, p>0.05), however, there was a trend that Group PII (Pantoprazole 30 mg 14 days) had the least leucocyte count and groups with *Aloe vera* showed higher lymphocyte count (Figure 4).

Discussion

The results demonstrated that the basal cell thickness ratio of the gastroesophageal junction (GEJ) in Sprague-Dawley rats with a GERD model was reduced following administration of *Aloe vera* extract at doses of 250 mg/kgBW and 500 mg/kgBW for 7 or 14 days are lower compared to the positive control group. However, no difference has been observed between the two treatment groups, indicating that the effect of Aloe vera on basal cell hyperplasia in this study is not dose-dependent.

The pathogenesis of esophageal mucosal inflammation in gastroesophageal reflux disease (GERD) has long been described as a "top-down" process, in which acid-peptic injury originates at the luminal surface. In GERD, several characteristic histopathological changes occur as a response to repeated mucosal damage. Continuous acid exposure diminishes the reparative capacity of the squamous epithelium, leading to abnormal epithelial differentiation and resulting in adaptive metaplasia that increases resistance to gastric reflux.[11]

Histological alterations include enhanced epithelial proliferation, such as basal cell hyperplasia, papillary elongation, and dilation of intercellular spaces, as well as inflammatory cell infiltration by eosinophils, neutrophils, and mononuclear cells within the epithelial layer.[12]

In GERD, reflux of acid and proteins, particularly pepsin, disrupts the tight junctions and adherens complexes between esophageal squamous cells. This disruption allows the hydrogen ions or acid to penetrate the epithelium, leading to cell death on the luminal surface. The death of surface epithelial cells may trigger an acute inflammatory response, characterized by infiltration of granulocytes and lymphocytes into the epithelium, and to stimulate a proliferative response in basal cells as they attempt to replace the damaged epithelial cells.[13] Histological features commonly observed in GERD, such as basal cell hyperplasia and elongation of squamous papillae, are thought to reflect this proliferative response to reflux-induced injury.[14]

Aloe vera extract may contribute to reducing vasoconstriction and enhancing capillary perfusion in the gastric mucosa, thereby accelerating ulcer healing. *Aloe vera* also

contains lectins, which are believed to inhibit gastric acid production, possibly through a direct action on acid-secreting cells.[15] As a result, the decreased acidity of the refluxate may prevent epithelial cell death, reduce acute inflammation, and limit the proliferative response in esophageal basal cells, hereby potentially preventing hyperplasia.[16,17]

Aloe vera extract also exhibits significant antioxidant activity, which contributes to ulcer healing and supports other biological processes involved in tissue repair. These include promoting wound healing, exerting anti-inflammatory, anticancer, and immunomodulatory effects, stimulating mucus secretion, and providing cytoprotective and gastroprotective properties.

Inflammation management remains a key factor in most healing processes. In addition, *Aloe vera* possesses immunomodulatory properties attributed to the polysaccharides in its gel, which help control gastric ulcer complications and demonstrate potential anticancer activity.[18]

However, this study shows no relationship between the dose of *Aloe vera* extract and lymphocyte count. The lymphocyte counts in the GEJ tissue of Aloe vera-treated GERD model rats (250 mg/kgBW and 500 mg/kgBW for 7 or 14 days) do not differ from either the positive or negative control groups, although a decreasing trend in lymphocyte count has been observed in the 14-day treatment group. In a related histological study where reflux esophagitis has been surgically induced in rats, allowing gastric and duodenal contents to flow freely into the esophagus, T-lymphocyte infiltration has been observed in the submucosa as early as three days post-operation.[18] By the first week, this infiltration has reached the lamina propria, and by the third week, the epithelial layer. Granulocyte infiltration typically became apparent around the fourth week.[19]

This study has a limitation. This is limitedprior research specifically examining the effects of *Aloe vera* on histopathological parameters in GERD models, which restricts direct comparison with previous findings Additionally, the specific bioactive compounds responsible for the observed effects were not isolated or quantified, limiting mechanistic interpretation.

In conclusion, *Aloe vera* extract at doses of 250 mg/kgBW and 500 mg/kgBW have a potential effect in reducing basal cells thickness in a Sprague-Dawley rat model induced by GERD but did not significantly reduced lymphocyte infiltration. These findings suggest that *Aloe vera* extract may have a supportive role as an adjuvant therapy in GERD management. Further studies are needed to confirm its effectiveness and underlying mechanisms. This study also underscores the importance of comprehensive GERD management, including healthy lifestyle promotion.

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Author's Contributions
SV conceptualized and designed the study, conducted the experiments, collected and analyzed the data, and drafted the manuscript; TD contributed to the study design, supervised the research process, and critically revised the manuscript; VV assisted in data interpretation, supervised the research process, and critically revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interest
The authors declare no conflicts of interest.

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Generative AI Disclosure Statement
No generative artificial intelligence (AI) tools were used in the design, analysis, or writing of this manuscript.

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