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Gastroprotective Effect of Galangal, Turmeric and Their Combination on Rats' Gastric Ulcers

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Abstract
Galangal (AG) and turmeric (CL) have potential gastroprotective activity. Both have been shown to prevent oxidation by scavenging free radicals and blocking oxidative enzymes. This study evaluated the gastroprotective effects of galangal, turmeric, and their combination extract against gastric mucosal lesions induced by ethanol-hydrochloric acid (HCl). The experimental design comprised 5 groups: group I was administered with Tween 80 (1%), and group II was administered ranitidine (50 mg/kgBW) orally. The other three groups were administered AG and CL, and their combination was administered (1:1) (100 mg/200 kg BW) orally for six days. On the 7th day, the rats were induced by ethanol-HCl (1: 1 v/v) 8 mL/KgBW. Six hours later, the rat was sacrificed and dissected for their gastric. Gross ulcer area, lesion length, histology, pH, and ulcer index were observed. There were improvements in pH, lesion score, ulcer index, and curative ratio. The histopathological profile showed ulcer repairment and lowering of neutrophil inflammatory cell infiltration. Statistical analysis showed the potential equivalence of the single and combination treatments in their gastroprotective effects. Galangal, turmeric, and its combination have gastroprotective activities by repair of ulcer and gastric pH, increasing the curative ratio, and decreasing the ulcer index in the rat model.

Keywords: galangal, gastroprotective, rats, turmeric

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Efek Gastroprotektif Lengkuas, Kunyit dan Kombinasinya terhadap Tukak Lambung Tikus

Abstrak
Lengkuas (AG) dan kunyit (CL) mempunyai potensi aktivitas gastroprotektif. Keduanya telah terbukti mencegah oksidasi dengan cara menangkap radikal bebas dan memblokir enzim oksidatif. Penelitian ini mengevaluasi efek gastroprotektif lengkuas, kunyit, dan ekstrak kombinasinya terhadap lesi mukosa lambung yang disebabkan oleh etanol - asam klorida (HCl) pada model tikus. Rancangan percobaan terdiri dari 5 kelompok, masing-masing kelompok terdiri dari 4 ekor tikus. Kelompok I diberikan Tween 80 (1%), kelompok II diberikan ranitidin (50 mg/kgBB) per oral. Tiga kelompok lainnya memberikan AG, CL, dan kombinasinya (1:1) (100 mg/200kgBB) secara oral. Seluruh kelompok diberi perlakuan selama enam hari dan pada hari ke-7 diinduksi dengan etanol-HCl (1:1) 8 mL/KgBB. Enam jam kemudian tikus dikorbankan dan dianalisis lambungnya. Area terjadinya ulkus, panjang lesi, histologi (pewarnaan H&E), pH, dan indeks ulkus diamati. Terdapat perbaikan pada pH, skor lesi, indeks ulkus, dan rasio kuratif. Profil histopatologi menunjukkan perbaikan ulkus dan penurunan infiltrasi sel inflamasi neutrofil. Analisis statistik menunjukkan potensi terapi tunggal dan kombinasi dalam efek gastroprotektifnya. Lengkuas, kunyit dan kombinasinya memiliki aktivitas gastroprotektif dengan memperbaiki tukak dan pH lambung, meningkatkan rasio kuratif, dan menurunkan indeks tukak pada model tikus.

Kata Kunci: gastroprotektif, kunyit, lengkuas, tikus

1. Introduction

Peptic Ulcer Disease (PUD) is a group of acid-peptic disorders in the upper gastrointestinal tract. It is defined as tissue loss or damage to the gastrointestinal mucosa that extends through the smooth muscle of the gastrointestinal tract.[1,2] This occurs due to an imbalance between gastric acid, pepsin, and mucosal defense factors.[3] Gastric damage by several compounds, including ethanol and HCl. Ethanol produces necrotizing lesions with a necrotizing action that directly reduces defensive factors such as bicarbonate and mucus production and increases acid secretion. While HCl can cause severe damage to the gastric mucosa.[4,5]

Gastric mucosal protection therapies commonly used are proton pump inhibitors (PPIs), antacids, and H2-receptor antagonists (H2RA).[6] However, types of conventional drugs used for gastric ulcers have side effects of arrhythmia, constipation, gynecomastia, hemopoietic changes, hypergastrinemia, hypocalcemia, impotence, and systemic alkalosis. Traditional medicine is an alternative to reduce the risk of drug side effects.[7]

Medicinal plants with potential anti-inflammatory activities include *Alpinia galanga* (AG) and *Curcuma longa* (CL). *A. galanga* contains 1'acetoxy chavicol acetate, flavonoids, and saponins.[8] 1'acetoxy chavicol acetate can slow or inhibit oxidation by scavenging free radicals and inhibiting oxidative enzymes produced during cell injury.[9] *A. galanga* juice at a dose of 16 mg/day could reduce inflammatory cells or inflammatory cells in the gastric histopathological appearance of male Wistar rats induced by mefenamic acid.[10]

Meanwhile, *C. longa* contains the main compound, namely curcumin. Curcumin, an antiulcer, works by inhibiting cyclooxygenase-2 (COX-2) and thromboxane A2 (TXA2) without affecting the activity of the COX-1 enzyme. This mechanism increases prostaglandin PGE2 synthesis and decreases inflammatory prostaglandin.[11,12] Ethanol extract of *C. Longa* doses of 100 and 200 mg/kgBW showed lower gastric ulcer scores than other doses.[13] The ethanolic extract of *C. longa* protects the stomach of rats from gastric ulcers after the stomach is induced by ethanol, as seen from the smaller total length of the lesion depending on the dose level.[14] *C. longa* infusion protects the gastric mucosa of rats against aspirin-gastric ulcers induced by rats.[15] According to how these two plants' active ingredients work, galangal prevents oxidation by snagging free radicals and blocking oxidative enzymes. Meanwhile, thromboxane A2 and cyclooxygenase-2 are inhibited by turmeric. The combination may have synergistic or additive effects.

Single use of galangal and turmeric demonstrates effectiveness in gastrointestinal protection. When galangal and turmeric ethanol extracts are combined, they ought to exert a synergistic impact as a gastroprotector which might overcome the drawbacks of single extracts or ranitidine. Therefore, the current study evaluated the gastroprotective activities of *Alpinia galanga, Curcuma longa,* and combination against ethanol-hydrochloric acid-induced gastric ulcer. Our study included pH measurements, lesion scores, ulcer indexes, curative ratios, and histological analyses that might not have been performed in previous studies.

2. Materials and Methods

2.1. Materials

Ethanol and hydrochloric acid (HCl) (Merck, Darmstadt, Germany) 60% 3 M; *Alpinia galanga* and *Curcuma longa* obtained from Centre of Research and Agricultural-Technological Study Manoko, Lembang, Bandung, West Java. The Rhizomes were authenticated in the Environmental Laboratory, Biology Faculty, Universitas Jenderal Soedirman. pH Meter Orion was used as an instrument.

2.2. Methods

2.2.1. Preparation of Alpinia galanga and Curcuma longa ethanol extract

A. galanga and *C. longa* rhizomes simplicia are washed with water, dried, and mashed into powder. Each powder, 500 grams, was macerated with 2.5 L of 96% ethanol for 1x24 h and filtered. The maceration was carried out for 3 x 24 h, and every 24 hours, it was changed and stirred. The macerate was evaporated using a rotary evaporator at a temperature of 60°C and a speed of 60 rpm to obtain a thick ethanolic extract. Ethanol is used because it is a universal solvent, volatile, does not affect, and can dissolve almost all polar, semi-polar, and non-polar substances.[16]

2.2.2. Experimental Animals

Animal-related experiments are permitted according to rules and regulations of the Animal Care Committee Faculty of Medicine, Universitas Jenderal Soedirman (certificate no. 272/KEPK/VII/2019).

Laboratory-bred Wistar albino rats (8 8-week-old and weighing 150 ± 30 g) obtained from Pharmacology Laboratory, Faculty of Pharmacy, University Muhammadiyah Purwokerto, Indonesia. The animals were maintained under standard laboratory conditions of 25°C and a photoperiod of 12 h dark and 12 h light. Commercial pellet diet and water provided ad libitum,

obtained from Clinical Pharmacy Laboratory Unsoed Purwokerto Indonesia. The animals were allowed to acclimatize for ten days before beginning the experiments.

2.2.3. Study Design

An experimental laboratory study was conducted from September to December 2019. A total of 20 male rats were randomized into five groups, namely the control and experimental groups. Each group consisted of 4 rats. The minimum group size derived from the formula (t-1) (r-1) >15, where t = the number of treatments and r = the number of rats.

Group I (negative control) was administered orally Tween 80 (1%), and group II (positive control) was administered ranitidine. The other three groups were administered *A. galanga* (AG), *C. longa* (CL), and a combination of AG and CL, 500 mg/KgBW for a single herb and 250 mg/KgBW for each combination herb, respectively.[14,17] Rats were treated according to their group for six days. On the 7th day, all groups were administered orally ethanol and hydrochloric acid at a dose of 8 mL/KgBW. After six hours, rats were sacrificed and dissected to take the stomach.

2.2.4. Score and Calculation for Ulcer Index, Curative Ratio and pH

Following surgery, the length and pH of the gastric mucosal lesion in the rats were measured. The lesion score, ulcer index, and curative ratio are calculated using the lesion length measurement results.

Score: 1 = <1,00 mm
2 = 1,00 – 2,00 mm
3 = 2,01 – 3,00 mm
4 = 3,01 – 4,00 mm
5 = 4,01 – 5,00 mm
10 = >5,00 mm
25 = perforation

Formula for ulcer index:

$$\text{Ulcer index} = \frac{\text{Total number of lesion scores}}{\text{Number of animal in each group}}$$

The rate of healing was calculated based on the curative ratio with the formula:

$$\text{Curative ratio}^{18} = \frac{a-b}{a} \times 100\%$$

Note:
a: Total score of ulcers in the negative control group
b: Total score of ulcers in treatment group

Meanwhile, the formula for pH calculation used for the analysis was:
$pH = -\log[H^+]$

2.2.5. Histopathologic Examination of Stomach Tissue

Following the animal sacrifice, the stomach of each rat was removed and fixed in 10% buffered formalin. After 12–24 h of fixation, 3–5 mm tissue slices were embedded in paraffin and stained with Hematoxylin (H) and Eosin (E) for histopathologic examination.

2.2.6. Data analysis

All results were represented as mean and standard deviation. Differences between groups were assessed by one-way analysis of variance (ANOVA), followed by Mann-Whitney test. Statistical significance defined as $p<0.05$ using SPSS 26.

The Shapiro-Wilk test, which included 50 samples' gastric pH values, was selected for the normality test. Upon determining the normal distribution, we performed the ANOVA statistical analysis to examine variations between the nominal data treatment groups. Since there were fewer than 50 samples and it was unnecessary to assume that the data were homogeneous and normally distributed, the Shapiro-Wilk distribution test and Kruskal Wallis statistical analysis were used to analyze the lesion score, ulcer index, and curative ratio data. The Mann Whitney test was then used.

3. Result

3.1. Ethanol Extract of Galangal and Turmeric Rhizome

In this study, the rhizomes of galangal and turmeric were extracted by maceration using a 96% ethanol solvent.The galangal rhizome ethanol extract yields 11.6%. On the other hand, the yield for the turmeric rhizome ethanol extract was 30.4% (Table 1).

3.2. Macroscopic Evaluation

Based on the macroscopy results, the tween-80 group showed the most severe gastric mucosal damage compared to the other groups. It was observed from the lesions in the stomach (Figure 1). Meanwhile,

Table 1. Ethanol Extract Yield for Turmeric and Galangal

Extract	Powder Weight (gram)	Thick Extract Weight (gram)	Yield (%)
Galangal Rhizomes	500	58	11.6
Turmeric Rhizomes	500	152	30.4

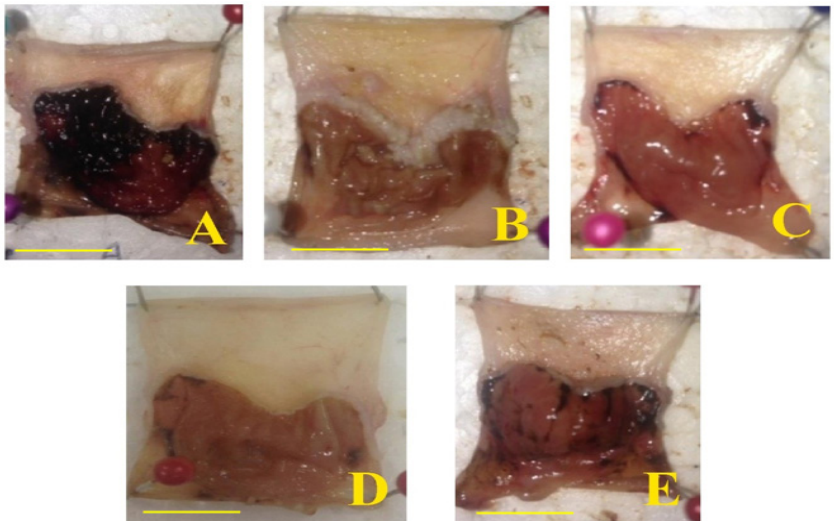

Figure 1. Gross appearance of the gastric mucosa in rats induced by HCl/EtOH. (A) Rats were administered with Tween 80. (B) Rats were administered 50 mg/KgBW Ranitidine. (C) Rats were administered 500 mg/KgBW of. (D) Rats were administered 500 mg/KgBW of. (E) Rats were administered 250 mg/KgBW of AG + 250 mg/KgBW of CL. AG: *A. galanga; CL: C. lon ga.* (Scale bar = 10 mm).

the ranitidine group showed smaller lesions than the extract group. The CL extract group showed smaller lesions compared to the AG extract and combination.

3.3. Effect of AG, CL and combination on lesion length

Based on the length of lesion data (Table 2), the tween-80 group showed the most severe gastric mucosal damage. This group showed the most lesion length compared to the other groups. These results showed that without any gastroprotective agent, the stomach mucosa will have severe damage caused by ethanol and hydrochloric acid. The CL group showed the shortest lesion length, significantly different from the tween-80 group. These indicated that CL had the most gastroprotective effect compared to the other

Table 2. Effect of AG, CL and combination on the length of lesion of gastric ulcer induced by EtOH/HCl on rats.

No.	Groups	Length (cm)	Average ± SD (n=4)
1.	I	1.62	1.99 ± 0.59
2.	Tween-80	1.26	
3.	(Negative ontrol)	2.79	
4.		2.28	
1.	II	1.07	1.24 ± 0.26*
2.	Ranitidine	0.94	
3.	(Positive Control)	1.63	
4.		1.33	
1.	III	0.22	1.25 ± 0.68*
2.	AG	2.12	
3.		1.42	
4.		1.25	
1.	IV	2.07	1.21 ± 0.54*
2.	CL	1.28	
3.		0.70	
4.		0.79	
1.	V	0.66	1.51 ± 0.71
2.	AG + CL	1.03	
3.		2.48	
4.		1.88	

* $p < 0.05$ versus negative control group by one-way analysis of variance with post hoc Mann Whitney. EtOH: Ethanol; AG: *A. galanga*; CL: *C. longa*

Table 3. Effect of AG, CL and combination on Ulcer Index and Curative Ratio of gastric ulcer induced by EtOH/HCl in rats.

No.	Groups	Lesi Score ± SD	Ulcer Index	Curative Ratio
1.	I	2 ± 0.57	2.50	0%
2.	Tween-80	2 ± 0.57		
3.	(Negative ontrol)	3 ± 0.57		
4.		3 ± 0.57		
1.	II	2 ± 0.50	1.75	30%
2.	Ranitidine	1 ± 0.50		
3.	(Positive Control)	2 ± 0.50		
4.		2 ± 0.50		
1.	III	1 ± 0.81	2.00	20%
2.	AG	3 ± 0.81		
3.		2 ± 0.81		
4.		2 ± 0.81		
1.	IV	3 ± 0.95	1.75	30%
2.	CL	2 ± 0.95		
3.		1 ±0.95		
4.		1 ± 0.95		
1.	V	1 ± 0.81	2.00	20%
2.	AG + CL	2 ± 0.81		
3.		3 ± 0.81		
4.		2 ± 0.81		

EtOH: Ethanol; AG: *A. galanga*; CL: *C. longa*

groups. Likewise, AG has a mean lesion length similar to CL. However, different results were shown in the AG + CL combination group. The average value of the lesion is shorter than tween-80 but longer compared with a single extract.

3.4. Effect of Galangal, Turmeric and Combination on Ulcer Index and Curative Ratio

The ulcer index value in the Tween 80 group showed the highest result (2.50) compared to other groups. Meanwhile, the CL extract group had a value of 1.75, the lowest value, the same as the ranitidine group. It showed that CL had the best gastroprotective activity, equivalent to ranitidine. Meanwhile, the combination group had an ulcer index value of 2, the same as the AG group (Table 3). It showed that the AG and CL combination had a lower gastroprotective effect than the CL extract.
The curative ratio (Table 3) indicated the healing rate of the ulcer. The value of the curative ratio indicates the healing rate. This means that the material has a gastroprotective effect. The curative ratio in the tween-80 group had the lowest value compared to other groups. It indicates that the Tween 80 group did not have a gastroprotective effect on the stomach of rats.

The curative ratio of the CL group was the highest (30%) of the ranitidine group. This indicates that CL has a gastroprotective activity equivalent to that of ranitidine. Meanwhile, the curative ratio of the combination group was the same as the AG group, which was 20%. It showed that the combination of AG and CL has a healing effect even though it is lower than CL.

3.5. Microscopic Evaluation

Figure 2 showed the histology of the rats' stomach with various treatments induced with ethanol/HCl. The tween-80 group showed acute inflammation of the lower gastric mucosa. There was a lot of infiltration of inflammatory cells, plasma lymphocytes, and PMNs. It is also seen as hemorrhagic in the submucosa, calcification, and severe ulcers. In addition, there is edema in the lamina propria and dilated blood capillaries.

The other treatment groups showed a reduction of lymphocytes, PMNs cells, neutrophil infiltration, hemorrhage, and ulcers. It indicates that all treatment groups other than the tween-80 group had a gastroprotective effect. The AG+CL combination group showed the lowest level of damage compared to other groups. The reduction in inflammatory cells of lymphocytes and PMNs also occurred greater than in other treatment groups. The combination

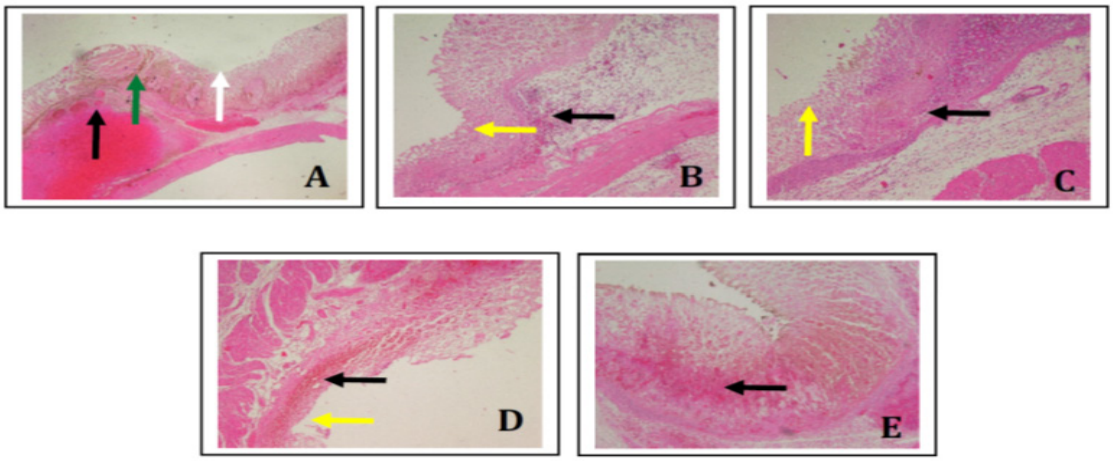

Figure 2. Effects of AG, CL, and combination on histopathological changes in the stomach of rats with ethanol/HCl-induced gastric ulcers. (A) Rats administered Tween-80. (B) Rats administered 50 mg/KgBW Ranitidine. (C) Rats administered 500 mg/KgBW of A. galanga. (D) Rats administered 500 mg/KgBW of C. longa. (E) Rats administered 250 mg/KgBW of AG + 250 mg/KgBW of CL. Histopathological changes were analyzed by H & E followed by observation at 40 times and 100 times magnification (group A and other groups, respectively). The black arrow indicates hemorrhage; the white arrow indicates necrosis; the green arrow indicates calcification; yellow indicates ulcer. AG: *A. galanga*; CL: *C. longa.*

group showed tissue recovery, indicated by many regenerated cells.

3.6. Effect of Galangal, Turmeric and Combination Extract on pH

Measurement data of gastric pH are shown in Table 4. The Tween-80 group has an average pH value smaller than the extract groups. The rat's stomach in the tween group showed high acidity levels.

From the three groups of extracts, it was found that the CL group had the best pH compared to the AG group and the combination of AG + CL. The value of gastric pH to maintain an acidic atmosphere is 2-3. It indicates that the pH values of all groups are still within the normal range. However, the negative control group is more acidic than the other groups, even though there was no statistically significant difference between the groups.

4. Discussion

Maceration immerses the sample to extract the desired component under discontinuous cold conditions. The benefit is that it doesn't require heating, is more practical, and uses less solvent but takes a long time. Alcohol works well as a solvent for initial extraction. In addition, ethanol may filter a variety of polarities, from polar to non-polar substances.[19]

When compared to the other groups, the tween-80 group displayed the most significant damage to the stomach mucosa. It was seen from the gastrointestinal lesions. In contrast, the ranitidine group displayed fewer lesions than the extract group. Compared to the AG extract and combination, the CL extract group displayed fewer lesions (Figure 1). These align with the literature that reported ethanol-HCl causes gastric lesions in rats.[20,21,22] Based on research by Raessi et al.,[4] oral administration of absolute ethanol affects gastric mucosa topically by interfering with the mucosal barrier and triggering microvascular changes within minutes of administration. Several studies used ethanol and hydrochloric acid to induce gastric ulcers. Ethanol is a necrotizing substance that produces necrotic lesions in the gastric mucosa and causes the blood cell's wall rupture. In addition, ethanol also causes hemorrhagic lesions, extensive submucosal edema, mucosal fragility, inflammatory cell infiltration, and epithelial cell loss in the stomach.[13,23,24]

The tween-80 group displayed the most serious damage to the stomach mucosa based on the length of the lesion data. In comparison to the other groups, this one displayed the longest lesion. These findings demonstrated that the stomach mucosa would suffer significant harm from ethanol and hydrochloric acid without any gastroprotective agent (Table 2). This result is similar to some research that reported *A. galanga* and *C. longa* has gastroprotective activity by reducing mucosal damage. These herbs reduce the damage that appears as a lesion in the stomach's mucosal.[10,13,25] Curcumin, the main component of *C. longa*, was also reported as gastroprotective by reducing mucosal damage in rats.[11] Similar to curcumin, 1,8-cineol as one of the main compounds of *A. galanga* has been reported to reduce the damage to rat-stomach's mucosal.[26] These findings suggest that although the combined AG and CL extract has less potency than the single extract, it still has a gastroprotective effect. The fact that the ideal dosage

Table 4. Effect of AG, CL and combination on pH of stomach induced by EtOH/HCl in rats.

No.	Groups	pH	Average ± SD
1.	I	2.50	3.28 ± 0.46
2.	Tween-80	3.40	
3.	(Negative ontrol)	3.50	
4.		3.70	
1.	II	3.30	3.18 ± 0.26
2.	Ranitidine	3.10	
3.	(Positive Control)	3.50	
4.		2.80	
1.	III	4.40	3.75 ± 0.77
2.	AG	2.60	
3.		3.50	
4.		4.50	
1.	IV	3.20	3.23 ± 0.48
2.	CL	2.70	
3.		3.00	
4.		4.00	
1.	V	3.00	3.43 ± 0.25
2.	AG + CL	3.60	
3.		3.50	
4.		3.60	

EtOH: Ethanol; AG: *A. galanga*; CL: *C. longa*

of the combination being utilized is yet unknown is one of the explanations behind this. Furthermore, because both of these rhizomes affect oxidative and cyclooxygenase enzymes, their effects might be similar.

Ulcer index value and curative ratio are used to determine the degree of gastric damage.[10] The lower the ulcer index value indicates less damage occurred. These showed that the Tween 80 group has no gastroprotective effect.[13] The curative ratio indicates the healing rate of the ulcer. The value of the curative ratio indicates the healing rate. It means the extract has a gastroprotective effect.[27] Ranitidine's molecular mechanism, in contrast to extracts, is to inhibit the H2 receptor, which lowers the formation of stomach acid. Both extracts, however, have anti-inflammatory properties that are proven to lessen the likelihood of lesions.

Alcohol is absorbed rapidly by the stomach and intestines. It induces endothelial vascular injury of the gastric mucosa, edema, congestion, spotting and focal bleeding, necrosis, and severe ulcers. It is due to the principal cell structure and gastric parietal cell, which contains a lot of mitochondria, swollen and damaged. Therefore, their number and function are drastically reduced. [28] There was a lot of infiltration of inflammatory cells of plasma lymphocytes and PMNs as seen in Figure 2. It is also seen as hemorrhagic in the submucosa, calcification, and severe ulcers. In addition, there is edema in the lamina propria and dilated blood capillaries. These results are in line with the research reported by Czekaj et al.[11] that the negative control group showed severe damage in the surface of the gastric epithelium, extensive edema in the submucosal layer, the presence of leukocyte infiltration and the formation of hemorrhagic lesions. Calcification occurs because ethanol causes an increase in the production of reactive oxygen species (ROS) and activates endoplasmic reticulum (ER) stress. It is another mechanism by which smooth muscle cells differentiate into osteoblast-like cells. Endoplasmic reticulum tension increases the expression of the transcription factor XBP-1 shown to bind to the Runx2 promoter and initiates differentiation and calcification.[29]

Cell regeneration is the formation of new cells to replace dead/damaged cells. The number of regenerating cells in the gastric mucosa of the combined group indicates that the tissue recovery process in this group occurs faster/earlier than in other groups. [30,31] It means the combination group has better gastroprotective activity than other treatment groups.

The rat's stomach in the tween 80 group had significant levels of acidity, and the group's average pH value was

lower than that of the extract groups. This suggests that the negative control generates the most acidic pH value because it has no gastroprotective impact on the rat's stomach.[32]

Our study design limitations include the short treatment duration, the absence of female animals, and the number of animals. It is preferable to test in larger animal models and examine the effects on chronic ulcers in future studies.

5. Conclusion

The anti-inflammatory properties of turmeric and galangal combination have a gastroprotective effect. Future research is required to investigate the impact on chronic ulcers.

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Conflict of Interest

The authors declare no conflicts of interest.

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