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Research Article

Effect Of 8% Ethyl Acetate Fractionated Coriander Seed (*Coriandrum sativum)* Extract Gel on The Number of Neutrophils and Fibroblasts in The Healing Process of Gingivitis (*in vivo* Study on Wistar Rats)

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KEYWORDS

Fibroblasts, gel extract coriander seed ethyl acetate fractionation, gingivitis, neutrophils.

ABSTRACT

Introduction: Gingivitis is inflammation of the gingiva and the initial stage of periodontal disease, which, if not treated, will become periodontitis. Coriander seeds (Coriandrum sativum) have anti-bacterial and anti-inflammatory properties. This study aimed to determine the effect of 8% ethyl acetate fractionated coriander seed extract gel on the number of neutrophils and fibroblasts in the healing process of gingivitis (in vivo) in Wistar rats.

Material and Method: Thirty-six rats were divided into 3 groups: the 8% ethyl acetate fractionated coriander seed extract gel group, the chlorhexidine gel group, and the placebo gel group. Gingivitis was induced by tying a silk ligation to the subgingival area of the lower incisor for 7 days. 0.05 ml of gel was applied twice a day in the gingivitis area. On days 1, 3, 5, and 7, three rats from each group were decapitated, histological preparations were made with HE staining, and the number of neutrophils and fibroblasts was counted using an Optilab microscope with 400x magnification. Healing assessment was measured based on the decrease in the number of neutrophils or the increase in the number of fibroblasts compared to the number of neutrophils or fibroblasts on the initial observation day.

Results and Discussions: A significant difference in neutrophil counts was found in the 8% ethyl acetate fractionated coriander seed extract gel group (45.43%) and the placebo gel group (51.67%) on days 3. A significant difference was also found in the number of fibroblast in the 8% ethyl acetate fractionated coriander seed extract gel group (5410%) and the placebo gel group (4470%) on days 5, and between the 8% ethyl acetate fractionated coriander seed extract gel group (8463.33%) and the placebo gel group (7953.33%) on days 7.

Conclusion: This research concludes that 8% ethyl acetate fractionated coriander seed extract gel can reduce the number of neutrophils and increase the number of fibroblasts in the gingivitis healing process.

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INTRODUCTION

Gingivitis is a mild periodontal disease often found in children. Its clinical symptoms include red, swollen gums that bleed easily without any damage to the alveolar bone.[1] Microscopically, gingivitis is characterized by inflammatory exudate and edema, damage to gingival collagen fibers, and ulceration and proliferation of the epithelium facing the tooth and attached to the gingiva.[2] The etiological factor of gingivitis is plaque bacteria.[3] The accumulation of a significant amount of plaque can lead to gingival inflammation, which begins with vascular changes due to capillary vessel dilatation and increased blood flow.[4] The initial stage of periodontal disease starts with inflammation of the gingiva (gingivitis) and, if not treated, it can progress to periodontitis.[5,6,7]

In the early stage of gingivitis, acute inflammation causes neutrophils to migrate to the gingival connective tissue, followed by monocytes that can differentiate into macrophages and perform phagocytize of bacteria. Neutrophils act as the body's first line of defense against foreign substances, particularly bacteria, and are the first cells to migrate to the infection site.[1,8] As inflammation begins to subside, the number of neutrophils gradually decreases, leading to the proliferative phase marked by migration of fibroblasts and deposition of the extracellular matrix. Fibroblasts play a crucial role in the healing process by synthesizing collagen fibers (connective tissue), which then allows for the regeneration of epithelial tissue.[9] Fibroblasts start to appear on the third day and peak on the seventh day.[10,11] In the final phase of healing, collagen synthesis and breakdown occur along with extracellular matrix remodeling.[11]

Gingivitis therapy involves eliminating the etiological factors through plaque control to reduce inflammation. Mechanical plaque control can be achieved through tooth brushing, scaling, and root planning. Clinically, gingivitis healing is indicated by reduced redness and swelling, while histologically, it is marked by a decrease in the number of PMN leukocytes and an increase in fibroblast migration.[4,5] In children, the ability to brush effectively to remove plaque is still very limited.[12] The gingivitis healing process can be aided by the use of chemical agents such as chlorhexidine, which is the gold standard. However, long-term use of chlorhexidine can cause yellowish-brown discoloration of the teeth, oral mucosa erosion, and temporary taste disturbances.[13] As an alternative, natural substances are now widely used in the form of mouthwash, gel, fiber, nanoparticles, and more. The use of gel formulations aims to ensure that the topical agent remains longer in the target area with a sufficiently high concentration.[14]

One such plant that can be used is coriander seeds (*Coriandrum sativum*), which contain essential oils, saponins, flavonoids, and tannins.[6] The essential oil contains 60-70% *d-linalool* and various other compounds.[9] *D-linalool* has antioxidant, anti-inflammatory, anticancer properties, and exhibits antibacterial activity against *Staphylococcus aureus* NCTC 10788, *Pseudomonas aeruginosa* NCTC 12924, and *Escherichia coli* NCTC 12923.[7] Ethyl acetate fractionation can extract the main active compound in coriander seed extract, which is *d-linalool*.[8] Previous studies have shown that an 8% concentration of coriander seed extract represents the highest MIC (Minimal Inhibitory Concentration) capable of inhibiting the growth of gram-negative and gram-positive bacteria, as well as *Candida*. According to a study by Lifia, coriander seed essential oil extract can inhibit the growth of *P. gingivalis*, one of the bacteria that cause gingivitis. Based on this background, further research is needed on the effects of 8% ethyl acetate fractionated coriander seed extract gel on the number of neutrophils and fibroblasts, which could then be used as an alternative topical agent to accelerate the healing process of gingivitis.

MATERIALS AND METHODS

This quasi-experimental laboratory study was approved by the Ethics Committee of the Faculty of Dentistry, Universitas Gadjah Mada (No. 198/UN1/KEP/FKG-RSGM/EC/2023). The research was conducted at the Central Integrated Research Laboratory (LPPT) unit IV FKH-UGM and the Integrated Research Laboratory of FKG UGM. A total of 36 male Wistar rats were divided into 3 groups, each consisting of 12 rats: the

8% ethyl acetate fractionated coriander seed extract gel group, the chlorhexidine gel group, and the placebo gel group.

The ethyl acetate fractionated coriander seed extract was prepared at the Laboratory of the Faculty of Pharmacy, Universitas Muhammadiyah Surakarta using the maceration technique. Coriander seeds were dried and ground into powder, then mixed with 70% ethanol using a homogenizer for 30 minutes and incubated for 24 hours. The solution was then filtered, and the residue was discarded while the active compounds were separated using a vacuum evaporator, resulting in the ethanolic extract of coriander seeds. Ethyl acetate fractionation was performed to separate compounds based on their solubility in solvents with different polarity levels. Ethyl acetate was evaporated at room temperature for 48 hours and then diluted to achieve an 8% concentration.

The gel was made by mixing the gel base (2% CMC-Na) with sterile distilled water to form a gel mass, then adding the ethyl acetate fractionated coriander seed extract, heating, and stirring for 10 minutes until homogeneous using a hot plate magnetic stirrer. The gel preparation was then allowed to cool before being placed into containers.

The rats were anesthetized with an intramuscular injection of ketamine HCl into the hind thigh muscle at a dose of 0.2 ml/200 grams of body weight. Gingivitis induction was performed by tying a 3.0 size silk ligature around the subgingival area of the lower anterior incisors. The ligature was left in place for 7 days to induce inflammation in the gingiva of the rats. The gingival status of the rats was assessed based on the Modified Gingival Index (MGI) by Lobene *et al.* (1986), with the expected inflammation being moderate.

Table 1. Scores and Criteria of the Modified Gingival Index (MGI) according to Lobene *et al*. [2]

Score	Inflammation	Keterangan
0	Normal	None
1	Mild inflammation	Slight changes in color and texture, but not in all portions of gingival marginal or papillary
2	Mild inflammation	Slight changes in color and texture in all portions of gingival marginal or papillary
3	Moderate	Bright surface inflammation, erythema, edema, and/or hypertrophy of gingival marginal or papillary
4	Severe inflammation	Erythema, edema, and/or marginal gingival hypertrophy of the unit or spontaneous bleeding, papillary, congestion, or ulceration

The gel application for each group was carried out using a syringe, 0.05 ml per application, administered twice daily, in the morning and evening. On days 1, 3, 5, and 7, three rats from each group were decapitated. The rats were injected with an overdose of ketamine and then decapitated using surgical scissors. The tissue collected was from the lower jaw area around the gingivitis site.

The lower jaw samples from the rats were cleaned with 0.9% NaCl solution and then fixed with 10% buffered formalin for 24 hours. Following fixation, the specimens were decalcified using 10% EDTA at 4°C. Subsequently, the gingiva from the labial side of the lower incisors was cut into 0,3-0,5 mm sections using a scalpel and placed into tissue cassettes. The samples underwent gradual dehydration sequentially with 70%, 80%, 90%, and absolute ethanol, each for 2 hours. After dehydration, the samples were cleared with xylol twice for 2 hours each and then degassed with a vacuum machine for 30 minutes. The tissues were embedded with liquid paraffin infiltration at 59-60°C into paraffin molds to form paraffin blocks and then stored in a freezer at -20°C. The blocks were sectioned using a microtome at a thickness of 5 µm, floated in a water bath at 50°C, and incubated on a hot plate for 15 minutes. The tissue sections were mounted on glass slides and stored in an incubator at 2-5°C below the paraffin melting point. Subsequently, the specimens were stained using Hematoxylin-Eosin (HE), rinsed under running water, and labeled. Microscopic examination at 400x magnification was performed to count the number of fibroblast and neutrophil cells observed in 4 fields of view. The final result was obtained by summing the counts from the four fields of view and calculating the average.

The data analysis method used involved testing normality of the data using the Shapiro-Wilk test and testing homogeneity using Levene's test. Data that were normally distributed and homogeneous were further

analyzed using *Repeated* ANOVA. To determine differences between each treatment group, LSD tests were conducted with a significance level of $p<0.05$ using SPSS software.

RESULTS AND DISCUSSION

The mean and standard deviation of neutrophil counts on observation days 1, 3, 5, and 7 for each treatment group are presented in Table 2. Table 3 presents the percentage or relative value of neutrophil counts on observation days 3, 5, and 7 compared to the neutrophil count on the first observation day, to assess the relative decrease compared to other treatment group.

Table 2. Mean and standard deviation of neutrophil counts

Treatment group	Observation day			
	1	3	5	7
P	68.75 ± 6.067	31.23 ± 4.289	2.25 ± 0.433	0
K+	68.91 ± 1.282	32.78 ± 3.381	2.55 ± 0.250	0
K-	96.41 ± 0.721	49.81 ± 1.808	3.85 ± 0.904	0

Description:
P: 8% Ethyl Acetate Fractionated Coriander Seed Extract Gel group
K+: chlorhexidine gel group
K-: placebo gel group

Table 3. Percentage reduction in neutrophil counts

Treatment group	Observation day			
	1	3	5	7
P	100%	45,43% ± 1,159	3,27% ± 0,854	0%
K+	100%	47,57% ± 5,229	3,70% ± 0,351	0%
K-	100%	51,67% ± 1,504	4,00% ± 0,954	0%

Tables 2 and 3 indicate a decrease in the number of neutrophils in all groups. On day 1, the neutrophil count in all groups is considered 100%. On days 3 and 5, the percentage of neutrophil count is lowest in the 8% ethyl acetate fractionated coriander seed extract gel group, and highest in the placebo gel group. On day 7, no neutrophils were found in any group. In the 8% ethyl acetate fractionated coriander seed extract gel group, the percentage decrease in neutrophil count was almost the same as in the chlorhexidine gel group. After conducting normality and homogeneity analyses, the significance values in all groups indicate significant results with $p>0.05$. This suggests that the data in this study have a normal and homogeneous distribution. Subsequently, a parametric test was conducted using *repeated* ANOVA, as shown in Table 4.

Table 4. Summary of the *repeated* ANOVA on the percentage of neutrophil count

	F	Sig.
Group	6.506	0.031
Observation Day	81744.235	0.000
Group * observation day	5.313	0.015

From Table 4, it can be concluded that the observation days, treatment groups, and interaction between these two variables have a significant impact on the percentage of neutrophil count. These finding indicate significant differences ($p<0.05$) in the percentage of neutrophil count in each treatment group. To further evaluate the differences between groups, a *Least Significant Difference* (LSD) test is conducted.

Table 5. Results of the LSD on the percentage of neutrophil count

	Significance
P3 – (K+3)	0.127
P3 – (K-3)	0.000*
(K+3) – (K-3)	0.006*

Description:
P3: 8% Ethyl Acetate Fractionated Coriander Seed Extract Gel group day 3
K+3: chlorhexidine gel group day 3
K-3: placebo gel group day 3
(*) Significance ($p<0,05$)

In Table 5, there is a significant difference ($p<0.05$) in the percentage of neutrophil count between the 8% ethyl acetate fractionated coriander seed extract gel group and the placebo gel group on day 3. A significant difference is also found between the chlorhexidine gel group and the placebo gel group on day 3. However, there is no significant differences in the percentage of neutrophil count between the 8% ethyl acetate fractionated coriander seed extract gel group and the chlorhexidine gel group on all observation days ($p>0.05$). Microscopic images of neutrophils in each group can be seen in Figure 1.

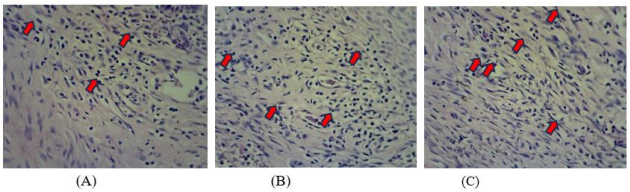

Figure 1. Microscopic appearance of neutrophils in all groups on day 3. The arrow indicate neutrophils; the number of neutrophils in the 8% ethyl acetate fractionated coriander seed extract gel group (A) is lower than in the chlorhexidine gel group (B) and the placebo gel group (C).

The mean and standard deviation of fibroblast count on days 1, 3, 5, and 7 for each treatment group can be seen in Table 6. Table 7 presents the percentage or relative value of fibroblast count on days 3, 5, and 7 compared to the fibroblast count on day 1 to assess the relative increase compared to other treatment groups.

Table 6. Mean and standard deviation of fibroblast count

	Observation day			
	1	3	5	7
P	3.00 ± 0.433	56.90 ±2.673	162.30 ± 2.068	253.89 ± 2.633
K+	3.00 ± 0.5000	55.29 ± 2.005	161.10 ± 4.125	248.30 ± 3.262
K-	2.75 ± 0.250	48.30 ± 1.010	122.90 ± 2.649	218.71 ± 5.444

Description:
P: 8% Ethyl Acetate Fractionated Coriander Seed Extract Gel group
K+: chlorhexidine gel group
K-: placebo gel group

Table 7. Percentage increase in fibroblast count based on treatment group and observation day

	Observation day			
	1	3	5	7
P	100%	1896.67% ± 0.873	5410% ± 2.946	8463.33% ± 0.665
K+	100%	1843.33% ± 0.838	5370% ± 2.511	8276.67% ± 7.538
K-	100%	1756.67% ± 0.680	4470% ± 1.200	7953.33% ± 0.757

The number of fibroblast in all groups increased over time (Tables 6 and 7). The percentage increase in fibroblast count was highest in the 8% ethyl acetate fractionated coriander seed extract gel group. In all groups, the highest percentage increase in fibroblast count was observed on day 7. The percentage increase in fibroblast count in the 8% ethyl acetate fractionated coriander seed extract gel group was nearly the same as in the chlorhexidine gel group.

Based on the results of normality and homogeneity tests, the significance values in all groups were significant, with $p>0.05$, indicating that the data were normally distributed and homogeneous. Subsequently, parametric test were conducted using *Repeated* ANOVA, and results of which can be seen in Table 8.

Table 8. Summary of the *Repeated* ANOVA on the percentage increase in fibroblast count

	F	Sig.
Group	22.677	.002
Observation day	19691.944	.000
Group * observation day	32.383	.000

Table 8 shows that there is significant relationship ($p<0.05$) between the observation days, treatment groups, and the interaction between these two variables on the percentage increase in fibroblast count. Furthermore, to determine the differences in the percentage increase in fibroblast count in each group, a *Least Significant Difference* (LSD) test was conducted, the results of which can be seen in Table 9.

Table 9. Results of the LSD on the percentage increase in fibroblast count

	Significance
P5 – (K+5)	0.847
P5 – (K-5)	0.000*
(K+5) – (K-5)	0.000*
P7 – (K+7)	0.373
P7 – (K-7)	0.025*
(K+7) – (K-7)	0.005*

Description:
P5: 8% Ethyl Acetate Fractionated Coriander Seed Extract Gel group day 5
P7: 8% Ethyl Acetate Fractionated Coriander Seed Extract Gel group day 7
K+5: chlorhexidine gel group day 5
K+7: chlorhexidine gel group day 7
K-5: placebo gel group day 5
K-7: placebo gel group day 7
(*) Significance($p<0,05$)

Table 9 shows that there is a significant differences ($p<0.05$) in the percentage increase in fibroblast count between the 8% ethyl acetate fractionated coriander seed extract gel group and the placebo gel group, as well as between the chlorhexidine gel group and the placebo gel group on days 5 and 7. However, there is no significant differences ($p>0.05$) between the 8% ethyl acetate fractionated coriander seed extract gel group and the chlorhexidine gel group on all observation days. Microscopic image of fibroblasts in each group can be seen in Figure 2.

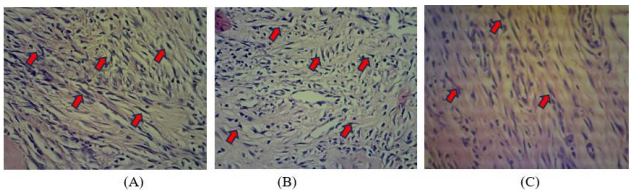

Figure 2. The microscopic appearance of fibroblasts in all groups on day 7. Arrows indicate fibroblasts; the number of fibroblasts in the group treated with 8% ethyl acetate fractionated coriander seed extract gel (A) is higher than those in the chlorhexidine gel (B) and placebo gel (C) groups.

This research aimed to gauge healing by observing the percentage decrease in neutrophil count and the percentage increase in fibroblast count compared to the initial counts. The findings suggest that applying 8% ethyl acetate fractionated coriander seed extract gel accelerates gingivitis healing by reducing the number of neutrophils and increasing the number of fibroblasts.

On day 1 of observation, neutrophil infiltration reaches its peak compared to the subsequent observation days. This is attributed to bacterial invasion into the tissue, triggering epithelial sulcus cells to secrete cytokines. These cytokines play a role in recruiting neutrophils, which then migrate to the tissue and phagocytose foreign substances. By day 3 of observation, the mean neutrophil count tends to decrease across all groups. When expressed as a percentage decrease, the 8% ethyl acetate fractionated coriander seed extract gel group shows the most significant reduction compared to the placebo gel group, with the lowest neutrophil count at 45.43%. This indicates that the use of 8% ethyl acetate fractionated coriander seed extract gel has a significant effect on reducing neutrophil count. These findings align with a study by Dillasamola[3] which concluded that ethanol extract of coriander seeds could enhance macrophage phagocytosis activity and reduce neutrophil count in male white rats at a dose of 200mg/kg. Conversely, the number of fibroblasts increases on the third day in all groups, although this increase does not show significant differences. This occurs because fibroblasts begin to proliferate on the third day.

On day 5 of observation, the inflammatory process continues to diminish, resulting in a further decrease in the percentage of neutrophils across all groups. However, there were no significant differences among the groups. This is because neutrophils have a short lifespan and are only found in the acute inflammatory phase, gradually being replaced by monocytes that differentiate into macrophages. Conversely, the percentage increase in fibroblast count on day 5 shows that the 8% ethyl acetate fractionated coriander seed extract gel group experienced the highest increase (5410%) and significantly differed from the placebo gel group.

On day 7 of observation, the percentage of neutrophils reached 0% as no neutrophils were found on that day. This occurred because the inflamed tissue had entered the next stage of healing, namely the proliferation phase. This phase is characterized by fibroblast migration stimulated by Transforming Growth Factor-β (TGF-β), which subsequently enhances collagen synthesis and extracellular matrix deposition. Conversely, the number of fibroblasts on day 7 will peak, with the highest percentage increase in fibroblast count observed in the 8% ethyl acetate fractionated coriander seed extract gel group. This difference is significant compared to the placebo gel group. In the placebo gel group, the percentage increase in fibroblast count is not as high as in the other groups because there are no triggers pushing for rapid proliferation to occur.

When examining the decrease in neutrophil count between day 3 and day 5, all groups show a nearly identical percentage decrease in neutrophils. This is because the tissue has entered the proliferation stage. Regarding the percentage increase in fibroblast count, the 8% ethyl acetate fractionated coriander seed extract gel group demonstrates a higher increase in fibroblast count compared to the placebo gel group. Looking at observations from day 5 to day 7, the percentage decrease in neutrophil count in all groups reaches 100%, resulting in neutrophil count dropping to 0. Meanwhile, concerning the percentage increase in fibroblast count, the placebo gel group shows a higher percentage increase compared to the 8% ethyl acetate fractionated coriander seed extract gel group. Nevertheless, the number of fibroblasts in the 8% ethyl acetate fractionated coriander seed extract gel group on day 7 remains the highest.

Based on the significant percentage decrease in neutrophil count and percentage increase in fibroblast count between the 8% ethyl acetate fractionated coriander

seed extract gel group and the placebo gel group, it can be concluded that the 8% ethyl acetate fractionated coriander seed extract gel has anti-inflammatory effects by reducing the number of neutrophils and increasing the number of fibroblasts. This is believed to be due to the presence of *d-linalool* in coriander seeds, further supported by GCMS (Gas Chromatography Mass Spectrometry) analysis, revealing that *d-linalool* constitutes the largest component in the coriander seed extract, accounting for 70.57%.

Several studies have shown that the compound *d-linalool* in coriander seeds has anti-inflammatory effects by controlling various inflammatory mediators and inflammatory cells such as neutrophils, dendritic cells, and macrophages. Research by Nair[15,16,17], concluded that the hydroalcoholic extract of Coriandrum sativum seeds has anti-inflammatory effects by reducing IL-6 levels in the treatment group compared to the control group.

D-linalool can interact with Nitric Oxide Synthase (NOS) to inhibit the production of nitric oxide without reducing enzyme synthesis. Nitric oxide regulates inflammatory and immune responses, contributing to the formation of edema, vasodilation, and the recruitment of immune cells at the site of inflammation. Additionally, *d-linalool* can reduce TNF-α-induced inflammation while inhibiting pro-inflammatory pathways caused by cytokine production (such as nitric oxide, NF-kB, TNF-α, IL-6, and IL-1β).[18,19,20]

Research conducted by Meilina[13], concluded that coriander seed extract ointment has significant activity in healing incised wounds in mice infected with *Staphylococcus aureus*. This is attributed to the d-linalool content in coriander seeds, which can enhance the activation and proliferation of fibroblasts, thereby promoting collagen formation and accelerating wound healing.[13]

In this study, chlorhexidine was used as a positive control because it remains the gold standard for gingivitis treatment. The results showed that the percentage decrease in neutrophils and increase in fibroblasts between the 8% ethyl acetate fractionated coriander seed extract gel group and the chlorhexidine gel group did not differ significantly. This is because both have antibacterial effects. *D-linalool* exhibits antibacterial activity against both Gram-positive and Gram-negative bacteria by disrupting bacterial cell membranes, leading to bacterial death. With the reduction in bacterial numbers, the inflammatory process diminishes, and the healing phase progresses more rapidly, thereby accelerating the healing of gingivitis.

The healing of gingivitis is marked by increased extracellular matrix metabolism and the activation and synthesis of TGF-β, which stimulates collagen biosynthesis and increases the number of fibroblasts. Histological examination shows a reduction in inflammatory cells such as neutrophils and macrophages, as well as an increase in fibroblasts by day 7. The results of this study indicate that in the group treated with 8% ethyl acetate fractionated coriander seed extract gel, the percentage of neutrophils was lower and the percentage increase in fibroblasts was higher compared to the placebo gel group. Although on day 5, the reduction in neutrophils was similar across all groups, healing in the group treated with the 8% ethyl acetate fractionated coriander seed extract gel occurred faster, by day 4. Therefore, it can be concluded that the gingivitis healing process in the 8% ethyl acetate fractionated coriander seed extract gel group occurred more rapidly, as evidenced by the reduction in neutrophils and the increase in fibroblasts. Further research is needed using additional parameters for gingivitis healing to strengthen these findings. Thus, the 8% ethyl acetate fractionated coriander seed extract gel can be developed as an effective alternative treatment to aid in the healing process of gingivitis.

CONCLUSION

Based on the research results regarding the effect of 8% ethyl acetate fractionated coriander seed extract gel on the number of neutrophils and fibroblasts in the healing process of gingivitis, it can be concluded that the application of 8% ethyl acetate fractionated coriander seed extract gel significantly reduces the number of neutrophils and increases the number of fibroblasts in the gingiva of rats with gingivitis.

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