

Effectiveness of Andaliman Fruit Extract Gel (*Zanthoxylum acanthopodium* DC.) 10% in Healing Recurrent Aphthous Stomatitis

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Abstract:

Background: Recurrent Aphthous Stomatitis (RAS) is a common oral mucosal disease. The treatment of RAS is challenging because the etiology remains unknown, and it is managed symptomatically. Andaliman fruit extract gel is one of the traditional remedies that can be used to treat RAS due to its antiinflammatory, antibacterial, and antioxidant effects, reducing pain and expediting the healing process. The purpose of this study was to determine the effectiveness of andaliman fruit extract gel 10% in RAS healing.

Materials and Methods: This research is a quasi-experimental research with pretest-posttest one group design. The sampling technique was done by purposive sampling. This study involved 16 active students of Faculty of Dentistry, University of North Sumatra who suffered from type RAS minor. Data collection was carried out by conducting an baseline of RAS by looking at halo erythema, ulcer size, and pain scale after treatment with andaliman fruit extract gel 10% and follow-up every day for the next three days. Data analysis in this study used Friedman test and Repeated Anova to determine differences in RAS observations before and after treatment.

Results: This study showed significant results on the reduction of halo erythema $p=0.000$ ($p<0.05$), ulcer size $p=0.000$ ($p<0.05$), and pain scale $p=0.000$ ($p<0.05$) in the baseline, first-day follow-up, second-day follow-up and third-day follow-up.

Conclusion: The conclusion of this study is that the administration of andaliman fruit extract gel 10% showed a significant reduction in halo erythema, ulcer size, and pain scale in RAS.

Key Word: Recurrent Aphthous Stomatitis, Andaliman, in Healing.

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I. Introduction

Recurrent Aphthous Stomatitis (RAS) is a common recurrent oral mucosal disease characterized by painful ulcers.¹ According to the 2018 Basic Health Research (Riskesdas), the prevalence of RAS at the national level was 8.0% and 9.1% in North Sumatra Province.² Recurrent Aphthous Stomatitis (RAS) is a very common oral mucosal disease characterized by painful, round or oval-shaped ulcers that recur, have clearly defined borders, are surrounded by a *halo* of erythema, and have a gray or yellowish base. Topical corticosteroid is the most commonly used chemical medications for treating RAS.^{3,4} However, these chemical medications can cause side effects. Therefore, there is a need to develop treatments for RAS using natural ingredients that may reduce the occurrence of these side effects. Andaliman (*Zanthoxylum acanthopodium* DC.) is a herbal medicine that could serve as an alternative treatment for RAS. Andaliman contains antiinflammatory, antioxidant, antibiotic, analgesic, antibacterial, and antifungal properties.⁵ This day, andaliman has frequently been used by the public as a natural alternative medication to treat various ailments, particularly for wound healing. Several researchers have conducted in vivo studies on Wistar rats regarding the healing of traumatic ulcers.⁶ However, no studies have yet examined whether andaliman can treat oral wounds. Based on this background, the researchers were interested in investigating the effectiveness of a andaliman fruit extract gel 10% in treating Recurrent Aphthous Stomatitis (RAS).

II. Material And Methods

A *quasi-experimental* study with a *one-group pretest-posttest design* was carried out on respondents of Department of Oral Medicine at the University of North Sumatra Dental and Oral Hospital in Medan from October to November 2023. A total 16 respondents (both male and females) of aged ≥ 18 years were for in this study.

Study Design: A *quasi-experimental* study with a *one-group pretest-posttest design*

Study Location: The sampling process for this case study was taken at the University of North Sumatra Dental and Oral Hospital in Medan

Study Duration: October to November 2023

Sample size: 16 respondents.

Subjects & selection method: Respondents first underwent a medical history review and clinical examination in University of North Sumatra Faculty of Dentistry Dental and Oral Hospital. Patients who met the clinical criteria for RAS minor were given an informed consent form and agreed to use the andaliman fruit extract gel 10%.

Inclusion criteria:

1. University of North Sumatra dental students with RAS minor who do not have systemic diseases such as *Behcet's syndrome* or *Crohn's disease*.
2. University of North Sumatra dental students with RAS minor who are not currently taking any medications.
3. University of North Sumatra dental students with RAS minor who are willing to sign an informed consent form.

Exclusion criteria:

1. University of North Sumatra dental students who wear braces and dentures.
2. University of North Sumatra dental students who uncooperative as research respondent.

Procedure methodology

This study began with the collection of andaliman from Pantis, Pahae Julu Subdistrict, North Tapanuli Regency, North Sumatra. The collected andaliman was washed, drained, and then dried. Once dry, they were ground in a blender to produce crude extract. The andaliman extract was prepared using the maceration method, which involved mixing 100 g of crude extract with 1 liter of 96% ethanol, stirring for the first 6 hours, and then allowing the mixture to stand for 18 hours. After that, filter the mixture and evaporate it using a rotary evaporator to obtain a concentrated extract. Andaliman fruit extract gel 10% is prepared by adding 96% ethanol dropwise to 10 grams of the concentrated andaliman extract, followed by the addition of a basic gel and stirring until homogeneous.

Data collection was conducted at the University of North Sumatra Faculty of Dentistry Dental and Oral Hospital. Respondents underwent medical history taking and clinical examination, if they met the eligibility criteria and were willing to participate, they signed an informed consent form. Respondents were given a andaliman fruit extract gel 10% at a dose of 3 times a day for 3 days. The gel was applied in a thin layer using a cotton swab in the morning (7:00 a.m.), at afternoon (1:00 p.m.), and in the evening (7:00 p.m.). This study involved baseline and follow-ups conducted over three consecutive days. The results of the observations were then recorded in the study's medical records.

Statistical analysis

Data was analyzed using SPSS version 20 (SPSS Inc., Chicago, IL). *Friedman test* and *repeated measures analysis of variance* (ANOVA) were used to analyze the results for *halo* erythema, ulcer size, and pain scale in RAS at baseline, the first-day follow-up, the second-day follow-up, and the third-day follow-up following the application of andaliman fruit extract gel 10% to the respondents.

III. Result

Table 1 : The demographic data of the study respondents, including the distribution and frequency of the sample by age. It can be seen that the study sample consisted of 16 respondents with RAS minor who were active students at the University of North Sumatra Faculty of Dentistry. The study included 13 respondents (81.3%) aged 18–22 years and 3 respondents (18.8%) aged 23–28 years who suffered from RAS minor.

Table 1 : Distribution and frequency of the sample by age based on RAS minor respondents.

No.	Age	Frequency (n)	Percentage (%)
1	18–22 years	13	81,3
2	23–28 years	3	18,8
Total		16 respondents	100%

Table 2 : Next, the demographic data of the study respondents the distribution and frequency of the sample by gender in this study. There were 16 respondents in this study. The respondents included 7 males (43.8%) and 9 females (56.3%) who suffered from RAS minor.

Table 2 : Distribution and frequency of the sample by gender based on type RAS minor respondents.

No.	Gender	Frequency (n)	Percentage (%)
1	Male	7	43,8
2	Female	9	56,3
Total		16 respondents	100%

Table 3 : The study data, based on the distribution and frequency of *halo* erythema, showed that during the baseline, 16 respondents (100%) exhibited *halo* erythema, while 0 respondents (0%) did not exhibited *halo* erythema. On the first-day follow-up, 13 respondents (81.3%) exhibited *halo* erythema, and 3 respondents (18.8%) did not exhibited *halo* erythema. On the second-day follow-up, 10 respondents (62.5%) exhibited *halo* erythema, and 6 respondents (37.5%) did not exhibited *halo* erythema. In the third-day follow-up, 6 respondents (37.5%) exhibited *halo* erythema, and 10 respondents (62.5%) did not exhibited *halo* erythema.

Table 3 : Distribution and frequency of *halo* erythema.

Halo Erythema	Halo Erythema				Total (%)
	Yes		No		
	n	%	n	%	
Baseline	16	100	0	0	100
First-day follow-up	13	81,3	3	18,8	100
Second-day follow-up	10	62,5	6	37,5	100
Third-day follow-up	6	37,5	10	62,5	100

Table 4 : Analysis of *halo* erythema using the *Friedman test* yielded a p-value=0.000 ($p<0.05$). $p<0.05$ indicates a significant difference, showing a significant reduction in type RAS minor *halo* erythema at the time of baseline, on the first-day follow-up, on the second-day follow-up, and on the third-day follow-up of the andaliman fruit extract gel 10%.

Table 4 : Analysis of RAS minor *halo* erythema results using the *Friedman test*

Halo Erythema	Mean	p-Value
Baseline	1,00	0.000*
First-day follow-up	1,19	
Second-day follow-up	1,38	
Third-day follow-up	1,63	

Note: *Significant ($p<0.05$)

Table 5 : The mean ulcer size in the 16 respondents with RAS minor at the time of baseline was $4.17 \text{ mm} \pm 1.97$. A reduction in ulcer size was observed after treatment with andaliman fruit extract gel 10%: $3.42 \text{ mm} \pm 1.99$ on the first-day follow-up, $2.71 \text{ mm} \pm 1.81$ on the second-day follow-up, and $1.78 \text{ mm} \pm 1.95$ on the third-day follow-up.

Table 5 : Mean ulcer size

Ulcers Size	Mean $\pm$ SD
Baseline	$4,17 \pm 1,97$
First-day follow-up	$3,42 \pm 1,99$
Second-day follow-up	$2,71 \pm 1,81$
Third-day follow-up	$1,78 \pm 1,95$

Table 6 : Analysis of ulcer size using a statistics test with *Repeated ANOVA* showed a p-value=0.000 ($p<0.05$). $p<0.05$ indicates a significant reduction the ulcer size in RAS minor at the time of baseline, the first-day follow-up, the second-day follow-up, and the third-day follow-up after treatment with andaliman fruit extract gel 10%. Based on this test, the results showed that the andaliman fruit extract gel 10% reduced ulcer size by an mean of 2.39 mm in three days.

Table 6 : Analysis of the results of ulcer size in RAS minor measurements using a *Repeated ANOVA*.

Ulcer Size	Mean $\pm$ SD	Mean Diff.	p-Value
Baseline	$4,17 \pm 1,97$	2,39	0.000*
First-day follow-up	$3,42 \pm 1,99$		
Second-day follow-up	$2,71 \pm 1,81$		
Third-day follow-up	$1,78 \pm 1,95$		

Note: *Significant ($p<0.05$)

Table 7 : The mean pain scale of 16 respondents with RAS minor at the time of baseline was 3.00 ± 0.89 . A reduction in pain scales was observed following treatment; the mean pain scale after application of andaliman fruit extract gel 10% was 2.13 ± 0.80 on the first-day follow-up, 1.38 ± 0.50 on the second-day follow-up, and 1.06

± 0.25 on the third-day follow-up.

Table 7 : Mean of pain scale

Pain Scale	Mean ± SD
Baseline	3,00 ± 0,89
First-day follow-up	2,13 ± 0,80
Second-day follow-up	1,38 ± 0,50
Third-day follow-up	1,06 ± 0,25

Table 8 : Statistical analysis using the *Friedman test* yielded a p-value=0.000. p<0.05 indicates a significant reduction in the type minor pain scale at the time of baseline, as well as during the first-day follow-up, second-day follow-up, and third-day follow-up after treatment with andaliman fruit extract gel 10%. Based on these results, it was found that the andaliman fruit extract gel 10% can reduce pain in RAS minor, with an mean decrease in the pain scale of 1.94 in three days.

Table 8 : Analysis of the results of the pain scale RAS minor measurements using the *Friedman test*.

Pain Scale	Mean ± SD	Mean Diff.	p-Value
Baseline	3,00 ± 0,89	1,94	0,000*
First-day follow-up	2,13 ± 0,80		
Second-day follow-up	1,38 ± 0,50		
Third-day follow-up	1,06 ± 0,25		

Note: *Significant (p<0.05)

IV. Discussion

The prevalence of RAS varies depending on the population studied. The prevalence of RAS ranges widely, from about 5% to 66%. The prevalence of RAS is estimated to be 25% worldwide.¹ RAS is very common among all respondents. However, it is most frequently observed during adolescence and is more common in females than in males (56.3% in females and 43.8% in males).⁷

This study included 16 respondents, of whom 13 (81.3%) were aged 18–22 years and 3 (18.8%) were aged 23–28 years and suffered from RAS. The results of this study indicate that RAS occurs in the 18–28 age group, which falls within the “young adult” category. This aligns with the study by Sulistiani *et.al.* which states that RAS is more prevalent during the second decade (ages 10–19) and third decade (ages 20–29).⁸ Kurniawati *et.al.* also demonstrated in their case study that RAS occurs more frequently during the second and third decades.⁹ These age groups are among the most vulnerable to RAS because they represent the most productive years of life, during which increased stress can trigger RAS. This study aligns with research by Safely *et.al.* which indicates that the incidence of RAS peaks between the ages of 20 and 29 and declines between the ages of 40 and 49.¹⁰

This study found that 7 men (43.8%) and 9 women (56.3%) participated as research respondents. The study shows that women experienced RAS more frequently than men. This is due to several predisposing factors that contribute to this occurrence, such as stress and menstruation.

Among the 16 dental student respondents, *halo* erythema was observed during the baseline; in 13 respondents, it was observed during the first-day follow-up; in 10 respondents, it was observed during the second-day follow-up; and in 6 respondents, it was observed during the third-day follow-up. The results of this statistical analysis indicate that the application of andaliman fruit extract gel 10% is effective in reducing *halo* erythema. The healing of *halo* erythema is preceded by cell migration and proliferation. Epithelial cells are the first to migrate to the center of the wound to prevent pathogen contamination. Fibroblasts then migrate to the subepithelial region and produce collagen to form replacement scar tissue, thereby inhibiting vasodilation and leading to the resolution of erythema. However, high concentrations of inflammatory cytokines (TNF-α and IL-6) inhibit the migration of epithelial cells and fibroblasts and increase levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), thereby creating a positive feedback loop for inflammation.¹¹ The flavonoid and alkaloid content in andaliman can suppress cyclooxygenase (COX) and lipoxygenase activity, thereby reducing the number of inflammatory mediators that can accelerate the reduction in erythema severity through a mechanism that inhibits the release of arachidonic acid.^{12,13}

The results of the ulcer size analysis in this study showed a reduction in ulcer size at the time of baseline, the first-day follow-up, the second-day follow-up, and the third-day follow-up. The mean ulcer size after application of the andaliman fruit extract gel 10% was 4.17 mm ± 1.97 at the baseline, 3.42 mm ± 1.99 at the first-day follow-up,

2.71 mm ± 1.81 at the second-day follow-up, and 1.78 mm ± 1.95 at the third-day follow-up. Bivariate analysis in this study, which used *Repeated ANOVA* to analyze ulcer size, showed a p-value=0.000 (p<0.05), indicating a significant difference in the size of type RAS minor ulcers. Andaliman can accelerate wound healing due to its antioxidant, antiinflammatory, and anti-microbial.¹⁴ The antioxidant properties derived from the

flavonoids in andaliman can suppress the infiltration of inflammatory cells, leading to faster wound healing. According to a study by Manurung *et.al.* the antioxidant properties of andaliman, which contain flavonoids, have been shown to reduce lipid peroxidation, thereby enhancing collagen viability and fibroblast proliferation, which can accelerate wound healing.¹⁵ The antiinflammatory properties of the flavonoids and alkaloids in the ethanol extract of andaliman can inhibit TNF- α , IL-6, and COX—which play a key role in the inflammatory process, thereby accelerating wound healing.^{5,12} The antibacterial properties of the alkaloids, flavonoids, and tannins in andaliman extract also help eliminate pathogenic microorganisms by causing bacterial cells to undergo lysis, a process that involves damaging the bacterial cell wall and increasing its permeability, leading to the leakage of intracellular bacterial metabolites.^{12,16}

The mean pain scale in this study, as measured by the *Verbal Descriptor Scale* at the time of baseline, was 3.00; the first-day follow-up was 2.13, on the second-day follow-up 1.38, and on the third-day follow-up 1.06. Based on this study, there was a decrease in the pain scale experienced by the respondents after the application of andaliman fruit extract gel 10%. The bivariate analysis in this study for ulcer size analysis used the *Friedman test*, which showed a p-value=0.000 ($p<0.05$), indicating a significant difference in the pain scale in RAS minor. The antiinflammatory mechanism of flavonoids and alkaloids works by directly inhibiting the activity of the COX and lipoxigenase enzymes, which leads to the inhibition of prostaglandin and leukotriene biosynthesis.¹²

V. Conclusion

The use of andaliman fruit extract gel (*Zanthoxylum acanthopodium* DC.) 10% is effective in reducing *halo* erythema, ulcer size, and pain scale in RAS minor.

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