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Comparative Efficacy of Zingiber officinale var. rubrum and Curcuma longa Supplementation in Protecting the Nasal Mucosa of Tobacco Smoke–Exposed Wistar Rats

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ABSTRACT: Tobacco smoke causes oxidative and inflammatory injury to the nasal mucosa. Red ginger (*Zingiber officinale var. rubrum*) and *Curcuma longa* have potential antioxidant and anti-inflammatory properties. This study compared their effects, alone and in combination, on nasal mucosal histopathology in tobacco smoke–exposed Wistar rats. In this randomized controlled experimental study, 36 Wistar rats were allocated to smoke-exposed control, red ginger, C. longa, or combination groups (n=9 per group). All animals received daily tobacco-smoke exposure for 28 days; treatment groups received the assigned botanical preparation orally. Nasal specimens were examined histopathologically, and MWHS was assessed. Group differences were analyzed using Kruskal–Wallis and chi-square tests. Mean total MWHS was highest in the red-ginger group (20.22 ± 2.68), followed by the *C. longa* group (20.00 ± 3.18), combination group (18.00 ± 2.78), and control group (17.89 ± 3.33). The overall difference was not statistically significant (p=0.206). Individual histopathological domains were also not significantly different among groups. Descriptively, red ginger was associated with more complete immature epithelialization and non-irregular collagenization, whereas *C. longa* showed the highest proportion of complete mature epithelialization. Red ginger and *C. longa* showed descriptive patterns of improved nasal mucosal repair after tobacco-smoke exposure; however, neither monotherapy nor the combination produced a statistically significant protective effect under the study protocol.

1. INTRODUCTION

Cigarette smoke contains oxidants and reactive aldehydes that disrupt nasal epithelial integrity, impair mucociliary function, and sustain local inflammation [1] . The nasal epithelium is a critical barrier whose repair requires coordinated epithelialization, stromal remodeling, angiogenesis, and inflammatory resolution [2] . Experimental rat models are useful for studying these processes because the rat nasal cavity has well-characterized regional anatomy and inhalation toxicology relevance [3] .

Curcuma longa is rich in curcuminoids with antioxidant and anti-inflammatory activity across multiple molecular targets [4] . In a rat model of nasal mucosal trauma, curcumin enhanced histological wound healing, supporting its potential in upper-airway tissue repair [5] . Red ginger (*Zingiber officinale var. rubrum*) contains gingerols and shogaols, compounds associated with modulation of inflammatory mediators and oxidative stress [6] . Curcuminoids principally modulate oxidative and inflammatory signaling, whereas gingerols and shogaols modulate inflammatory mediators and oxidative stress through partially distinct pathways; direct comparison of the two monotherapies and their combination was therefore designed to assess whether these profiles translate into differential or additive histopathological effects [4,6].

Although each botanical has biologically plausible protective properties, comparative evidence in tobacco-smoke-exposed nasal mucosa is limited. A prior experimental report found oral curcumin protective after electric-cigarette exposure, but the effects of red ginger and a combined regimen after tobacco smoke remain uncertain [7] . We therefore compared red ginger, Curcuma longa, and their combination on histopathological repair of tobacco-smoke-exposed nasal mucosa in Wistar rats.

2. MATERIALS AND METHODS

2.1 Study Design, Setting, dan Materials

This randomized controlled experimental animal study was conducted from March to July 2026. Animal acclimatization, tobacco-smoke exposure, and intervention administration were performed at Doc Pet Clinic, Makassar, Indonesia. Histopathological preparation and examination were performed at Iris Education Veterinary Laboratory, Makassar, Indonesia.

The study materials included tobacco cigarettes, a smoking chamber connected to an air pump and oxygen source, commercial red ginger (*Zingiber officinale var. rubrum*) extract, and commercial Curcuma longa preparation (PT Shizen, Indonesia). Additional materials included standard rat feed, drinking water, 10% formalin, histological reagents, glass slides, coverslips, and specimen containers. Histopathological examination was performed using a binocular microscope (XSZ-107BN). The botanical interventions were administered as commercially prepared products supplied by PT Shizen; no independent plant authentication, extraction procedure, or assay of active constituents was undertaken. Accordingly, the findings apply to the stated commercial preparations rather than to chemically standardized extracts.

2.2 Animals and Eligibility Criteria

Thirty-six healthy Wistar rats (*Rattus norvegicus*), aged 3–4 months and weighing 150–200 g, were included. The minimum required sample size was calculated using the Federer formula, which indicated at least nine evaluable animals per group. Eligible animals were healthy, had no anatomical nasal abnormalities, and showed no evidence of rhinitis at baseline examination. Animals with diarrhea, nasal-cavity narrowing, marked body-weight loss, suspected allergic or toxic reactions, or death during the study period were excluded from the final analysis. Eligibility was assessed before allocation by baseline physical and rhinoscopic examination.

2.3 Housing and Acclimatization

Animals were housed individually in clean cages under ambient temperatures of 28–32°C, with adequate ventilation and light exposure. Standard feed and drinking water were supplied ad libitum. Before allocation, all rats underwent a 7-day acclimatization period and baseline physical and rhinoscopic examination.

2.4 Randomization and Study Groups

Following acclimatization, rats were assigned by simple randomization to four groups, with nine rats in each group. All groups received daily tobacco-smoke exposure for 28 consecutive days. The smoke-exposed control group received no botanical treatment. The red-ginger group received oral *Z. officinale var. rubrum* extract by gavage. The *C. longa* group received oral *C. longa* by gavage. The combination group received both *Z. officinale var. rubrum* and *C. longa* orally by gavage. Botanical preparations were administered concurrently with daily tobacco-smoke exposure. Allocation was performed after baseline assessment using simple randomization, with equal allocation to the four study groups; no stratification or blocking was used.

2.5 Tobacco-Smoke Exposure

For each exposure session, rats were placed in the smoking chamber. Tobacco cigarettes were connected through tubing to an air pump, ignited, and the smoke was directed into the chamber. Oxygen was simultaneously supplied to the chamber at the

protocol-specified setting of 0.5 ppm. Each group was exposed to smoke generated from 2–3 tobacco cigarettes daily for 28 days.

2.6 Intervention Administration

Red ginger and *C. longa* preparations were administered orally using a gavage tube throughout the 28-day exposure period. The extracts were prepared in an appropriate vehicle before administration. Doses were calculated according to individual body weight when required by the final study protocol, and administration was performed once daily during the tobacco-smoke exposure period. The administration schedule was once daily for 28 consecutive days. The archived study records contain inconsistent dose units across sections; consequently, exact dose values cannot be reported reliably without verification against the original animal-treatment log.

2.7 Tissue Collection and Histological Processing

After completion of the intervention period, animals were anesthetized. Nasal secretions were aspirated, and the nasal region was prepared using aseptic and antiseptic procedures. Nasal tissue was collected by rhinotomy at levels II–III of the nasal cavity and placed immediately in 10% formalin. Fixed specimens underwent routine histological processing and hematoxylin–eosin staining. Slides were deparaffinized in xylene, rehydrated through graded alcohol solutions, stained with eosin and hematoxylin, dehydrated, cleared in xylene, mounted with Entellan, and covered with coverslips. The prepared slides were examined at 400× magnification.

2.8 Histopathological Outcome Assessment

Nasal mucosal repair was assessed using the MWHS. The evaluated domains were epithelialization, collagenization, inflammatory-cell infiltration, neovascularization, necrosis, and granulation tissue formation. Each domain was scored from 1 to 5 according to the degree of tissue repair, with higher scores indicating more favorable histopathological healing. Total MWHS was calculated as the principal comparative outcome. Histopathological processing and assessment were performed at a separate veterinary laboratory; however, blinding of the assessor to treatment allocation was not documented in the original protocol.

2.9 Statistical Analysis

Data were analyzed using SPSS and RStudio. Descriptive data were presented as mean ± standard deviation for total MWHS and as frequencies and percentages for categorical histopathological findings. Differences in total MWHS among the four groups were assessed using the Kruskal–Wallis test. Categorical histopathological variables were compared using the chi-square test. All tests were two-sided, and $p<0.05$ was considered statistically significant. Exact p values for the overall and pairwise analyses are reported in Tables 1–3. Categorical outcomes were analyzed as frequency distributions, and the pairwise comparisons were considered exploratory because the overall comparisons were not statistically significant.

3. RESULTS AND DISCUSSION

3.1 Study Sample and Histopathological Findings

Thirty-six Wistar rats were included in the analysis, with nine animals in each study group. The overall mean MWHS was 19.03 ± 3.07. Across all specimens, complete immature epithelialization was the most frequent epithelial finding (50.0%), whereas complete mature epithelialization was observed in 13.9% of specimens. Complete non-irregular collagenization was present in 52.8% of specimens, and mild inflammation was observed in 50.0%. Focal necrosis was identified in 38.9% of specimens, whereas 61.1% showed no necrosis.

3.2 Comparison of Total MWHS Across Study Groups

Total MWHS differed numerically among groups; however, the overall difference was not statistically significant (Kruskal–Wallis p=0.206; Table 1 and Figure 1). The red-ginger group had the highest mean score (20.22 ± 2.68), followed by the *C. longa* group (20.00 ± 3.18). The combination group had a mean score of 18.00 ± 2.78, whereas the smoke-exposed control group had the lowest mean score (17.89 ± 3.33).

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Table 1. Total Modified Wound Healing Score by study group (n=9)

Study group	Total MWHS, mean ± SD	P value
Smoke-exposed control	17.89 ± 3.33	0.206
Red ginger	20.22 ± 2.68	
Curcuma longa	20.00 ± 3.18	
Red ginger + *C. longa*	18.00 ± 2.78	

P value from the Kruskal–Wallis test.

3.3 Comparison of Histopathological Findings Across the Four Groups

No significant between-group difference was identified for epithelialization, collagenization, inflammation, neovascularization, necrosis, or granulation tissue formation (all p>0.05; Table 2).

Table 2. Key histopathological findings across study groups

Histopathological domain	Control	Red ginger	*C. longa*	Combination	P value
Partial epithelialization	5 (55.6)	1 (11.1)	4 (44.4)	3 (33.3)	0.119
Complete immature epithelialization	3 (33.3)	7 (77.8)	2 (22.2)	6 (66.7)	
Complete mature epithelialization	1 (11.1)	1 (11.1)	3 (33.3)	0 (0.0)	
Partial collagenization	5 (55.6)	1 (11.1)	3 (33.3)	5 (55.6)	0.454
Complete non-irregular collagenization	3 (33.3)	7 (77.8)	5 (55.6)	4 (44.4)	
Mild inflammation	5 (55.6)	3 (33.3)	4 (44.4)	6 (66.7)	0.286
No inflammation	1 (11.1)	4 (44.4)	4 (44.4)	0 (0.0)	
Neovascularization <5 vessels/HPF	3 (33.3)	6 (66.7)	4 (44.4)	6 (66.7)	0.483
Focal necrosis	5 (55.6)	†	3 (33.3)	4 (44.4)	0.668
Mature moderate granulation	2 (22.2)	†	4 (44.4)	3 (33.3)	0.856

Values are n (%). P values were calculated using the chi-square test. HPF, high-power field. †Verify the red-ginger raw data before submission because the source table totals 10 observations despite the reported group size of 9.

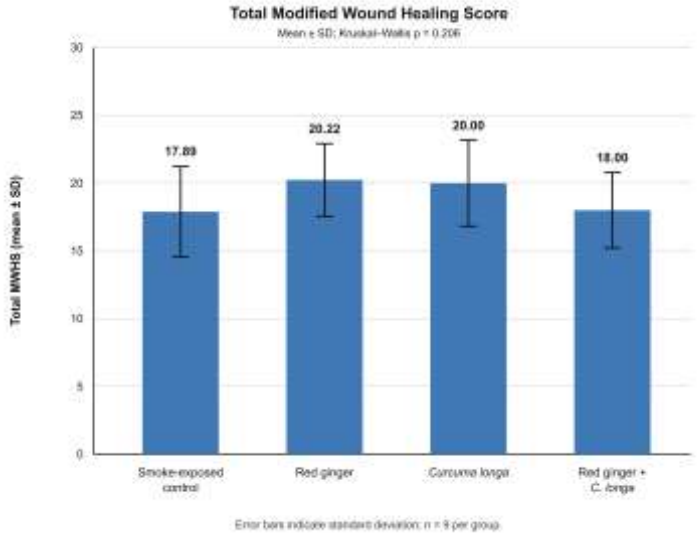


Figure 1. Mean total Modified Wound Healing Score by study group. Error bars indicate standard deviation; n=9 per group. Kruskal–Wallis p=0.206.

Nevertheless, descriptive differences were observed. Partial epithelialization was most frequent in the control group (55.6%), whereas complete immature epithelialization was most frequent in the red-ginger group (77.8%) and combination group (66.7%). Complete mature epithelialization was most frequent in the C. longa group (33.3%).

Complete non-irregular collagenization was most frequent in the red-ginger group (77.8%), followed by the *C. longa* group (55.6%). The absence of inflammation was observed in 44.4% of animals receiving red ginger or C. longa, whereas mild inflammation was most frequent in the combination group (66.7%). The control group had the highest proportion of focal necrosis (55.6%). These descriptive patterns did not demonstrate statistically significant treatment effects.

3.4 Pairwise Comparisons Between the Control and Treatment Groups

Compared with the smoke-exposed control group, the red-ginger group showed a higher proportion of complete immature epithelialization and complete non-irregular collagenization, together with a greater proportion of specimens without inflammation. However, none of the histopathological domains differed significantly between the two groups (all $p \geq 0.205$; Table 3). Compared with the control group, the C. longa group showed a higher proportion of complete mature epithelialization (33.3% vs 11.1%), complete non-irregular collagenization (55.6% vs 33.3%), and absence of inflammation (44.4% vs 11.1%). No significant differences were observed in any histopathological domain (all $p \geq 0.240$; Table 3). The combination group showed more complete immature epithelialization than the control group (66.7% vs 33.3%) and a higher proportion of neovascularization below five vessels per high-power field (66.7% vs 33.3%). Nevertheless, all comparisons between the combination and control groups were non-significant (all $p \geq 0.347$; Table 3).

Table 3. Pairwise comparisons of histopathological domains

Comparison	Epithelialization	Collagenization	Inflammation	Neovascularization	Necrosis	Granulation
Control vs red ginger	0.205	0.205	0.482	0.347	0.335	0.827
Control vs *C. longa*	0.689	0.798	0.240	0.637	0.637	0.562
Control vs combination	0.347	1.000	1.000	0.347	1.000	1.000
Red ginger vs *C. longa*	0.102	0.772	1.000	0.637	1.000	1.000
Red ginger vs combination	0.576	0.131	0.136	1.000	0.620	0.698
***C. longa* vs combination**	0.097	0.637	0.154	0.637	1.000	0.256

Values are p values from chi-square tests.

3.5 Pairwise Comparisons Between Treatment Groups

The red-ginger group showed a higher proportion of complete immature epithelialization than the C. longa group (77.8% vs 22.2%), whereas complete mature epithelialization was more frequent in the *C. longa* group (33.3% vs 11.1%). The difference in epithelialization approached, but did not reach, statistical significance ($p=0.102$). All other histopathological domains were also non-significant. Compared with the combination group, the red-ginger group showed numerically higher proportions of complete non-irregular collagenization and absence of inflammation. Conversely, the combination group showed a higher

proportion of mild inflammation. These differences were not statistically significant. Compared with the combination group, the *C. longa* group had a higher proportion of complete mature epithelialization and absence of inflammation. The combination group had a higher proportion of complete immature epithelialization. No statistically significant difference was observed between these groups, including for epithelialization (p=0.097).

3.6 Discussion

Tobacco smoke contains oxidants, reactive aldehydes, and other toxic compounds that disrupt epithelial integrity and sustain inflammatory injury in the nasal mucosa. The histopathological pattern observed in the smoke-exposed control group is consistent with evidence that cigarette smoke impairs epithelial homeostasis, mucociliary function, and tissue repair through oxidative stress and local inflammatory activation [1,8] . The persistence of partial epithelialization, incomplete collagenization, inflammation, and focal necrosis in this group supports the relevance of this model for examining tobacco smoke–associated nasal mucosal injury.

Although the overall between-group difference in MWHS was not statistically significant, red ginger and *C. longa* monotherapy showed descriptive patterns of improved mucosal repair compared with the smoke-exposed control. Red ginger was associated with more advanced epithelial and collagen repair, a pattern that is biologically plausible given the anti-inflammatory and antioxidant activities of gingerols and shogaols. These compounds may reduce inflammatory mediator production and oxidative injury through modulation of prostaglandin, leukotriene, cyclooxygenase-2, inducible nitric oxide synthase, and nuclear factor kappa B signaling [6,9] .

The *C. longa* group showed a descriptive tendency toward more mature epithelialization. This finding is in line with Emiroglu et al. (2017) [5] , who reported improved healing in a rat model of nasal mucosal trauma after curcumin administration. It is also consistent with the antioxidant and anti-inflammatory properties of curcuminoids, which may support epithelial regeneration and collagen deposition by reducing oxidative stress and proinflammatory cytokine activity [4,10] . Similarly, Syahreza et al. (2025) reported a protective effect of oral curcumin on the nasal mucosa of Wistar rats exposed to electronic-cigarette smoke [7] .

The combination regimen did not show a descriptive advantage over either monotherapy. This finding suggests that simultaneous administration of red ginger and *C. longa* did not produce an additive histopathological effect under the present protocol. Herbal combinations do not necessarily result in synergistic activity because interactions among bioactive compounds may alter absorption, metabolism, or downstream biological activity. Therefore, the present findings support the possibility that red ginger and *C. longa* may have distinct effects on mucosal repair rather than a clearly enhanced effect when administered together.

Taken together, the findings suggest that red ginger may preferentially support epithelial and collagen repair, whereas *C. longa* may be associated with epithelial maturation. However, these observations should be interpreted as descriptive biological signals rather than evidence of confirmed therapeutic efficacy, because no significant differences were identified across the evaluated histopathological outcomes.

The analysis used a small number of animals per group and was based on semiquantitative histopathology. Concurrent daily smoke exposure may have obscured repair during treatment, and oral delivery may have limited local bioavailability. The source documents also contain inconsistent dose units; these must be reconciled with the laboratory record before submission. The sample size may have limited power to detect small-to-moderate between-group effects, and the unblinded histopathological assessment may have introduced observer bias. These factors should be considered when interpreting the non-significant findings.

4. CONCLUSION

In this tobacco smoke–exposed Wistar rat model, red ginger and Curcuma longa monotherapy showed descriptive patterns of improved nasal mucosal repair, including epithelial recovery, collagen formation, reduced inflammatory changes, and less necrosis. Red ginger showed a tendency toward more advanced epithelial and collagen repair, whereas C. longa showed a tendency toward greater epithelial maturation. However, neither monotherapy nor their combination produced statistically significant differences in MWHS or individual histopathological outcomes compared with the smoke-exposed control group.

The combination regimen showed no additive protective effect. Overall, these findings do not establish protective efficacy; they provide preliminary observations that warrant dose-verified, adequately powered, and blinded follow-up studies.

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AUTHOR CONTRIBUTIONS

M.U.: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing—original draft. A.Q.P.: Conceptualization, Methodology, Supervision, Writing—review and editing. S.P.R.: Methodology, Validation, Investigation, Writing—review and editing. M.F.P.: Methodology, Investigation, Formal analysis, Writing—review and editing. A.T.R.: Investigation, Data curation, Writing—review and editing. A.A.Z.: Methodology, Validation, Writing—review and editing. N.I.D.: Methodology, Validation, Writing—review and editing. A.A.: Supervision, Validation, Writing—review and editing. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS STATEMENT

The protocol was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Hasanuddin (No. 454/UN4.6.4.5.31/PP36/2026; approved March 30, 2026). All animal procedures were conducted in accordance with the approved protocol.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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