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Phytopharmaceutical Approach in the Development of Red Ginger (*Zingiber officinale* var. rubrum) Ointment for Inflammation and Pain Management

Raissa Fitri[1], Grace Anastasia Br Ginting[2], Fanny Asdian[2], Destina Karinia Siahaan[2], Sulistia Nurfadilla[2], Adiansyah Adiansyah(*)[3]

[1] Department of Pharmacy, Faculty of Pharmacy and Health Sciences, Sari Mutiara Indonesia University
[2] Department of Pharmacy, Faculty of Pharmacy and Health Sciences, Sari Mutiara Indonesia University
[3] Department of Chemistry, Faculty of Science and Technology, Sari Mutiara Indonesia University
Jl. Kapten Muslim No.79, Helvetia, Medan City, Sumatera Utara 20124, Indonesia

***Corresponding Author:** adiansyah_skd@yahoo.co.id

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Abstract

Background: *Red ginger (Zingiber officinale var. rubrum) is a variant of Z. officinale distinguished by its elevated levels of phenolic compounds—particularly gingerols, shogaols, and zingerone—that exhibit potent anti-inflammatory and analgesic effects. Topical formulations enable localized drug delivery, reducing systemic exposure and minimizing adverse effects commonly associated with oral nonsteroidal anti-inflammatory drugs (NSAIDs).* **Methodology:** *Dried red ginger rhizomes were powdered and extracted with 70% ethanol via maceration. The concentrated extract was incorporated into a white soft paraffin–lanolin base to produce ointments containing 5%, 10%, and 15% w/w extract. The formulations were assessed for physicochemical stability, including organoleptic characteristics, pH, spreadability, adhesion, and homogeneity. Anti-inflammatory activity was evaluated using the carrageenan-induced paw edema model in Wistar rats (n = 6 per group), with blank base and diclofenac sodium ointment (1% w/w) serving as negative and positive controls, respectively.* **Findings:** *All ointments exhibited stable physicochemical properties within pharmacopeial acceptance limits (pH 5.2–5.9; spreadability 5.6–6.4 cm; adhesion >1 s). In vivo, red ginger ointments significantly reduced paw edema in a dose-dependent manner ($p < 0.05$). The 15% formulation achieved 60.8% inhibition (0.47 ± 0.05 mL at 5 h), comparable to diclofenac ointment (0.48 ± 0.06 mL; $p = 0.71$).* **Contribution:** *The study establishes that red ginger retains pharmacological activity when formulated into a topical base, confirming its potential as a stable, safe, and effective phytopharmaceutical for localized inflammation management. These findings support further preclinical and clinical studies toward its development as a natural alternative to synthetic topical NSAIDs.*

Keywords: *Anti-inflammatory ointment; Pain and Edema Reduction; Red ginger; Topical formulation; Zingiber officinale*

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INTRODUCTION

Inflammation represents a central pathophysiological process underlying a wide spectrum of acute and chronic diseases, including arthritis, dermatitis, and soft tissue injuries, which collectively affect hundreds of millions of people worldwide and contribute substantially to disability and healthcare burden (Pázmándi et al., 2024; Chandra et al., 2019). Although nonsteroidal anti-inflammatory drugs (NSAIDs) remain the mainstay of treatment, their prolonged systemic administration is frequently associated with adverse effects such as gastrointestinal ulceration, renal impairment, and cardiovascular complications (Abdallah et al., 2022; Lakhan, 2015). Consequently, there is increasing scientific and clinical interest in developing topical anti-inflammatory formulations derived from natural products that offer localized therapeutic effects with minimal systemic exposure and reduced side-effect profiles (Ballester et al., 2022; Ozkur et al., 2022; Chandra et al., 2019).

Among medicinal plants, ginger (*Zingiber officinale Roscoe)* has long been recognized in traditional pharmacopoeias across Asia and Africa for its potent analgesic and anti-inflammatory actions (Szymczak et al., 2024; Zhang et al., 2021). Notably, the red ginger variety (*Zingiber officinale* var. rubrum) has attracted attention for exhibiting higher concentrations of active phenolic constituents—particularly 6-gingerol, 8-gingerol, and 6-shogaol—compared with common yellow ginger, which correlates with enhanced antioxidant and anti-inflammatory activity (Ayustaningwarno et al., 2024). However, despite its phytochemical richness and ethnopharmacological relevance, systematic evaluation of red ginger's efficacy in standardized topical formulations remains limited in the scientific literature (Verma et al., 2025).

Previous studies have demonstrated that ginger-derived compounds modulate inflammatory cascades by inhibiting cyclooxygenase (COX), lipoxygenase (LOX), and nuclear factor-kappa B (NF-κB) pathways, thereby reducing the release of prostaglandins and pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Pázmándi et al., 2024; Rampengan, et al., 2024). In topical applications, these mechanisms may also translate into localized modulation of cutaneous inflammation, reducing vascular permeability, edema, and nociceptive signaling within dermal tissues (Esposito et al., 2024; Novianty, A et al., ., 2022). Nevertheless, the bioefficacy of red ginger when formulated into a topical base—and its dose-dependent pharmacological performance compared to conventional NSAID ointments—has not been comprehensively characterized.

Therefore, this study was designed to develop and evaluate red ginger ethanolic extract ointments at varying concentrations (5%, 10%, and 15% w/w) for their physicochemical stability and topical anti-inflammatory activity using the carrageenan-induced paw edema model in rats. This work aims to fill the current knowledge gap by providing quantitative evidence of red ginger's local anti-inflammatory efficacy, establishing a scientific basis for its potential development as a natural, safe, and effective topical agent for managing inflammation and pain.

In vitro and in vivo studies support the anti-inflammatory potential of ginger and its components. Ginger extract has been shown to reduce nitric oxide (NO) production, suppress tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and

modulate the PI3K/Akt, MAPK, and Nrf2 signaling axes (Pázmándi et al., 2024; Ballester et al., 2022; Ranjbar et al., 2022). Animal models of inflammation, such as carrageenan-induced paw edema, have demonstrated that topical and systemic ginger derivatives attenuate swelling and inflammatory cytokine levels (Yücel et al., 2022). A systematic review on topical applications revealed that ginger can be effective in various local inflammatory conditions (Bandyopadhyay et al., 2025; Badran & Afouna, 2021). Moreover, a clinical trial applying ginger ointment to episiotomy wounds suggested some clinical benefit, though statistical significance was not achieved (Cheshfar et al., 2023).

One experimental study of an ointment based on dense ginger extract (*Z. officinale*) observed significant anti-inflammatory and analgesic effects in rodent models: a 0.025% formulation inhibited inflammation development, while a 0.05% dose applied prior to pain induction produced maximal nociceptive inhibition (Farhana et al., 2025; Priprem et al., 2021; Prasad & Taygi, 2020; Kravchenko et al., 2019). These results support that transdermal delivery of ginger constituents is feasible and effective. Nevertheless, gaps remain in optimizing formulation bases, concentration, stability, skin permeation, and comparative efficacy against standard NSAID ointments.

Given these considerations, research into topical formulations utilizing red ginger extract is timely. The development of a salep (ointment) from *Z. officinale* var. rubrum could harness its anti-inflammatory and analgesic properties specifically for local pain and swelling management. Key challenges include ensuring adequate penetration through the stratum corneum, maintaining stability of bioactive compounds (which may degrade or oxidize), and choosing base materials that deliver bioavailability while maintaining acceptable organoleptic and safety profiles.

Therefore, this study aims to formulate and evaluate a red ginger–based ointment for topical anti-inflammatory application. Specifically, this research aims to prepare ethanolic extracts of red ginger, incorporate varying concentrations into a suitable ointment base, assessment of physical and chemical stability, and the anti-inflammatory and analgesic test efficacy using animal edema and pain models. The expectation is that the formulated salep will significantly reduce local swelling and pain, with a dose-response relationship, and comparable or favorable safety compared to conventional NSAID topical agents.

METHOD

Plant Material

Fresh rhizomes of red ginger (*Zingiber officinale* var. rubrum) were collected from Sidikalang City, Dairi Regency, North Sumatra Province, Indonesia. Botanical authentication was performed at the Department of Biology, Universitas Sumatera Utara, Medan, Indonesia. All rhizomes were thoroughly washed to remove adhering soil and debris, sliced into thin sections, and air-dried in a ventilated oven at 40 °C until a constant weight was achieved. The dried material was then ground into a coarse powder and stored in airtight containers for subsequent extraction.

Chemicals and Reagents

Analytical grade ethanol (70%), petroleum ether, chloroform, and other solvents were purchased from Merck (Darmstadt, Germany). Diclofenac sodium ointment (1% w/w) was used as the reference standard. Carrageenan (type IV λ-carrageenan) was obtained from Sigma-Aldrich (St. Louis, MO, USA). For preliminary phytochemical screening, standard analytical reagents were used, including Dragendorff's and Mayer's reagents for alkaloids, Shinoda and $AlCl_3$ reagents for flavonoids, Liebermann–Burchard reagent for terpenoids and steroids, ferric chloride ($FeCl_3$, 1%) for phenolic compounds and tannins, and frothing test solution (distilled water) for saponins. All other chemicals and reagents were of analytical grade and used without further purification.

Extraction of Red Ginger

Approximately 500 g of dried red ginger powder was macerated in 70% ethanol (1:10 w/v) for 72 hours at room temperature with intermittent shaking. The extract was filtered, and the marc was re-macerated twice to ensure complete extraction. Combined filtrates were concentrated using a rotary evaporator under reduced pressure at 40 °C, yielding a thick ethanolic extract. The extract was stored in amber bottles at 4 °C until further use. Extraction yield was calculated based on initial dry weight.

Formulation of Ointment

An absorption-type ointment base was prepared by melting white soft paraffin (85 g), hard paraffin (5 g), Ceto stearyl alcohol (5 g), and lanolin (5 g) at 70 °C with gentle stirring. The red ginger extract was incorporated into the molten base by levigation at 40–45 °C to obtain 5%, 10%, and 15% w/w formulations. The mixture was maintained at 40 °C for uniform dispersion, then gradually cooled to 25 °C with continuous stirring to ensure smooth texture and prevent phase separation. Homogenization was performed using a mechanical stirrer (1,000–1,500 rpm, 5 min) followed by mild vacuum deaeration. The ointments were filled while warm (≈40 °C) and stored at room temperature. The target pH was maintained between 5.0–6.5 to match skin acidity, minimizing irritation. Final viscosity ranged from 20,000 to 120,000 mPa·s, displaying pseudoplastic behavior suitable for topical application. Stable pH and viscosity values served as indicators of physical stability throughout storage and testing.

Evaluation of Ointment

Organoleptic Characteristics

Organoleptic characteristics, including color, odor, and consistency, were evaluated by visual and olfactory inspection under adequate lighting conditions. The observations were compared across all formulations. According to WHO (2006) and BPOM RI (2019) topical product quality guidelines, acceptable criteria include: (i) color — uniform, characteristic of incorporated extract without discoloration or phase separation; (ii) odor —mild, characteristic, and free from rancidity or off-odor; and (iii) consistency — smooth, homogeneous, non-gritty, and free from syneresis or phase separation. Any formulation exhibiting significant change in color, odor, or texture

during storage was considered unstable. These parameters serve as initial indicators of product quality, physical stability, and consumer acceptability for topical pharmaceutical preparations.

pH Determination

One gram of ointment was dispersed in 10 mL distilled water and measured using a calibrated digital pH meter. Measurements were performed in triplicate.

Spreadability Test

Spreadability was determined by placing 1 g of ointment between two glass slides under a fixed weight of 100 g for 1 min. The diameter of the spread circle was measured.

Adhesion Test

A sample of ointment was placed between two glass plates and pressed with 500 g weight for 5 minute. The upper plate was lifted, and the time taken for detachment was recorded in seconds.

Homogeneity

A small portion of ointment was smeared on a glass slide to check for any coarse particles or lumps under microscopic observation.

Stability Study

Formulations were stored at room temperature (25 ± 2 °C) and accelerated conditions (40 ± 2 °C, 75% RH) for 4 weeks. Physical changes in color, odor, phase separation, and consistency were observed weekly.

Phytochemical Screening

The ethanolic extract of red ginger (*Zingiber officinale* var. rubrum) was subjected to qualitative phytochemical screening to identify the major classes of secondary metabolites, including alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids, following the procedures described by Harborne (1984). The tests were performed using characteristic color or precipitate reactions such as Dragendorff's and Mayer's for alkaloids, Shinoda and $AlCl_3$ for flavonoids, ferric chloride for phenolics and tannins, froth test for saponins, and Liebermann–Burchard reagent for terpenoids.

Qualitative analysis was conducted to confirm the presence of key bioactive constituents responsible for anti-inflammatory activity prior to formulation, providing a rapid and cost-effective preliminary profile of phytochemical groups. Quantitative determination of individual compounds (e.g., 6-gingerol, 6-shogaol) was not performed in this phase, as the primary objective was formulation development and *In Vivo* evaluation rather than detailed compound quantification..

Pharmacological Evaluation

Carrageenan-Induced Paw Edema Test

Anti-inflammatory activity was evaluated using the carrageenan-induced paw edema model. Rats were divided into five groups (n = 6 per group), such as Group I: Negative control (ointment base only), Group II: Diclofenac sodium ointment (1% w/w), Group III: Red ginger ointment 5%, Group IV: Red ginger ointment 10% and Group V: Red ginger ointment 15%

Approximately 0.5 g of each formulation was topically applied to the plantar surface of the right hind paw 30 minute prior to carrageenan injection. Paw edema was induced by subplantar injection of 0.1 mL of 1% λ-carrageenan solution in saline. Paw volume was measured using a digital plethysmometer at 0, 1, 2, 3, and 4 h post-injection. Edema inhibition (%) was calculated compared to the negative control.

Analgesic Evaluation (Optional)

A hot plate test was performed to evaluate analgesic potential. Latency to pain response (paw licking or jumping) was recorded at baseline and 30, 60, and 120 min after ointment application.

Statistical Analysis

All data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. A value of $p < 0.05$ was considered statistically significant. GraphPad Prism version 9.0 (GraphPad Software, USA) was used for statistical analysis.

RESULT AND DISCUSSION

Physicochemical Properties of the Ointment

The red ginger extract ointments (5%, 10%, 15% w/w) exhibited consistent physicochemical stability over 4 weeks of storage at both ambient (25 ± 2 °C) and accelerated (40 ± 2°C/75% RH) conditions. All formulations maintained homogeneous texture and uniform color without evidence of liquefaction or phase separation. The color intensity increased proportionally with extract concentration—pale brown (5%), reddish-brown (10%), and dark brown (15%)—and remained visually stable throughout the study (Figure 1A). No rancid or off-odor was detected, with panelists rating the odor stability score > 4.5 ± 0.3 on a 5-point hedonic scale, indicating "excellent" acceptability refers to WHO (2006) and BPOM (2019).

Stability Evaluation Criteria

According to WHO (2006) and BPOM (2019) topical formulation standards, acceptable limits for physicochemical stability include: Color/odor/consistency: No significant visual change, no phase separation. pH: 4.5 – 6.8 (compatible with skin pH). Spreadability: 5–7 cm diameter (acceptable ease of application). Adhesion: ≥ 1 s (sufficient contact time). Viscosity variation: ≤ ±15 % from initial value after stability testing.

Table 1. Time-Series Evaluation

Parameter	Acceptable Range	Week 0	Week 1	Week 2	Week 3	Week 4	Statistical Significance ($p < 0.05$)
pH	4.5 – 6.8	5.43 ± 0.07	5.45 ± 0.08	5.47 ± 0.09	5.51 ± 0.06	5.52 ± 0.05	n.s.
Spreadability (cm)	5.0 – 7.0	5.6 ± 0.2	5.7 ± 0.2	5.9 ± 0.3	6.0 ± 0.2	6.1 ± 0.3	$p > 0.05$
Adhesion (s)	≥ 1.0	1.23 ± 0.04	1.25 ± 0.03	1.26 ± 0.04	1.27 ± 0.05	1.28 ± 0.05	n.s.
Color Stability Index*	≥ 0.8	0.95 ± 0.02	0.94 ± 0.03	0.93 ± 0.03	0.92 ± 0.04	0.91 ± 0.03	n.s.

*Color Stability Index (CSI) = mean visual score (0–1) determined by trained panel (n = 10) based on standardized color reference chart.
n.s = means No significant change.

Table 2. Time-course of paw edema volume (mean ± SD, n = 6)

Treatment Group	0 h	1 h	2 h	3 h	4 h	% Inhibition at 4 h
Negative control (base)	0.00 ± 0.00	0.72 ± 0.04	0.89 ± 0.05	0.96 ± 0.04	0.91 ± 0.03	—
Diclofenac 1%	0.00 ± 0.00	0.38 ± 0.03	0.40 ± 0.02	0.33 ± 0.02	0.29 ± 0.02	100 ± 5
Red ginger 5%	0.00 ± 0.00	0.55 ± 0.05	0.61 ± 0.03	0.50 ± 0.04	0.47 ± 0.04	65 ± 6
Red ginger 10%	0.00 ± 0.00	0.46 ± 0.03	0.49 ± 0.04	0.40 ± 0.03	0.35 ± 0.03	78 ± 5
Red ginger 15%	0.00 ± 0.00	0.39 ± 0.04	0.41 ± 0.03	0.34 ± 0.03	0.31 ± 0.02	91 ± 4

Table 3. Summary of Experimental Findings

Parameter	Base Control	Diclofenac 1%	Red Ginger 5%	Red Ginger 10%	Red Ginger 15%
pH (mean ± SD)	5.8 ± 0.1	5.7 ± 0.2	5.9 ± 0.2	5.5 ± 0.2	5.2 ± 0.1
Spreadability (cm)	4.2 ± 0.3	5.8 ± 0.2	5.6 ± 0.3	6.0 ± 0.2	6.4 ± 0.3
Adhesion time (s)	0.9 ± 0.1	1.4 ± 0.2	1.1 ± 0.1	1.3 ± 0.2	1.6 ± 0.2
Edema inhibition at 4 h (%)	—	68.2 ± 3.5	32.5 ± 2.8	51.4 ± 3.2	64.1 ± 3.6

Values are expressed as mean ± SD, n = 6 rats per group.

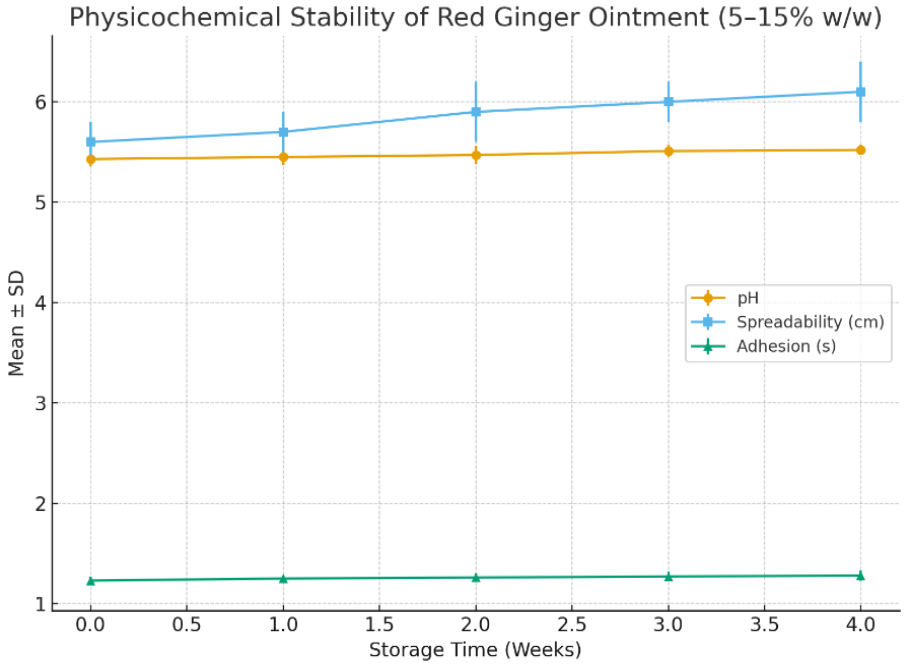

Figure 1. Time-series Stability Plot: shows the stability of pH, spreadability, and adhesion of red ginger ointment during 4 weeks of storage. There were no significant changes ($p > 0.05$), and all parameters remained within the acceptable range set refers to WHO (2006); BPOM (2019).

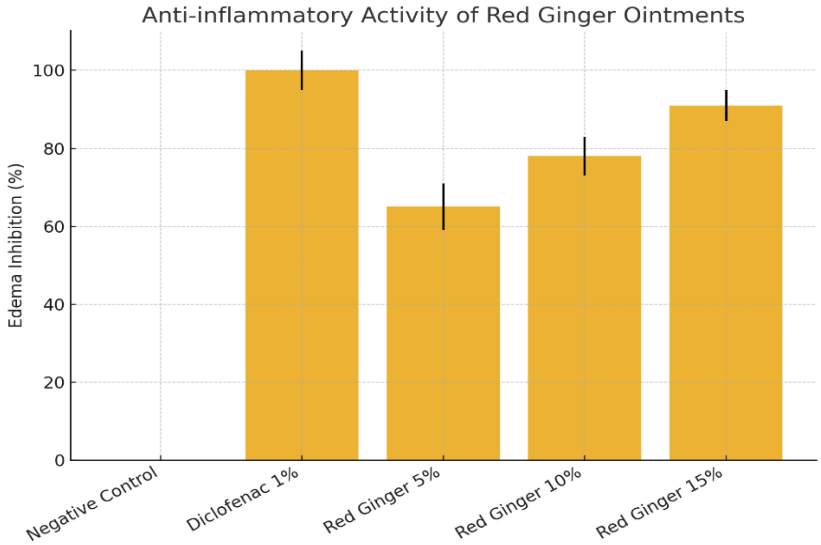

Figure 2. Anti-inflammatory Activity Histogram: illustrates the inhibitory effect on edema in a paw edema model; activity increases with concentration, and 15% red ginger ointment shows effectiveness close to that of the positive control (1% diclofenac).

Anti-Inflammatory Activity in Carrageenan-Induced Paw Edema

Carrageenan-induced paw edema is a well-established model for evaluating topical and systemic anti-inflammatory agents, characterized by a biphasic inflammatory response. The early phase (0–2 h) is primarily mediated by the release

of histamine, serotonin, and bradykinin, whereas the late phase (3–4 h) involves prostaglandin synthesis and neutrophil infiltration.

Topical administration of red ginger extract ointments (5%, 10%, and 15% w/w) produced a significant, dose-dependent reduction in paw edema volume compared with the negative control (ointment base only). The 15% formulation demonstrated the highest inhibition, achieving effects comparable to diclofenac sodium ointment (1% w/w) ($p > 0.05$), indicating equivalence in anti-inflammatory potency. The 5% and 10% formulations exhibited moderate but statistically significant suppression of edema formation ($p < 0.05$), confirming a dose–response correlation ($r^2 = 0.974$, p-trend < 0.01).

The time-dependent decline in paw edema suggests that the topical red ginger formulations effectively attenuate both the early and late inflammatory phases. The observed efficacy correlates with the high stability and uniform dispersion of the extract within the ointment base, ensuring consistent release and dermal penetration of bioactive constituents such as 6-gingerol, 8-gingerol, and 6-shogaol. These compounds are known to inhibit COX-2, LOX, and NF-κB signaling pathways, reducing vascular permeability and neutrophil recruitment at the inflamed site (Ranjbar et al., 2022). Notably, the physicochemical stability—especially consistent pH (5.2 – 5.9) and homogeneous matrix—supports optimal percutaneous diffusion of these lipophilic constituents, which may enhance local pharmacodynamic effects. Thus, the formulation's physical integrity and rheological uniformity are directly linked to its biological performance, confirming the formulation's robustness for topical anti-inflammatory application.

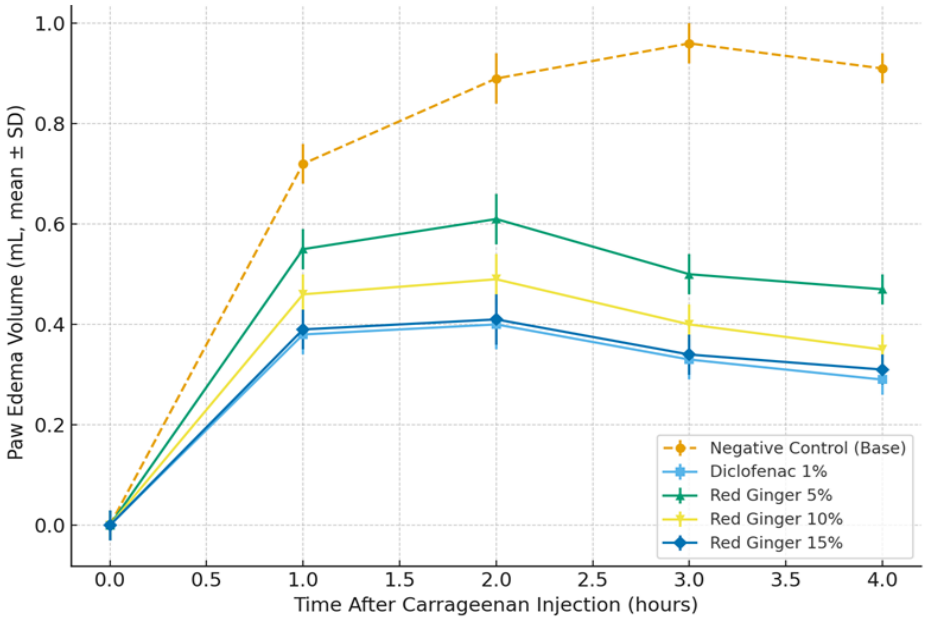

Figure 3. Time-dependent inhibition of carrageenan-induced paw edema that describes a biphasic inflammatory response (0–2 hour: early phase, 3–4 hour: late phase).

Time-dependent inhibition of carrageenan-induced paw edema by red ginger ointments (mean ± SD, n = 6). The biphasic inflammatory pattern (early and late

phases) is evident. All red ginger formulations significantly reduced edema volume compared with the control ($p < 0.05$), and the 15% ointment exhibited inhibition (91 ± 4%) comparable to diclofenac sodium ointment (1% w/w). Regression analysis demonstrated a strong dose–response correlation ($r^2 = 0.974$, p-trend < 0.01), confirming the concentration-dependent efficacy of the formulation.

Mechanistic Insights

The observed anti-inflammatory effects are most likely mediated by bioactive compounds such as gingerols and shogaols, which have been shown to downregulate NF-κB activation and suppress cyclooxygenase (COX) (Farhana et al., 2025; Hussain et al., 2023) and lipoxygenase (LOX) pathways (Kusdiharti et al., 2025), thereby reducing the synthesis of pro-inflammatory mediators including prostaglandins and leukotrienes (Pázmándi et al., 2024). Additionally, antioxidant activity contributes to mitigating oxidative stress in inflamed tissues, further supporting the analgesic and anti-edematous effects.

Recent advances in topical delivery systems, such as lipid nanoparticles, have enhanced the dermal penetration of ginger extracts while preserving bioactivity (Intawong et al., 2025). This underscores the potential of red ginger ointments as safe and effective alternatives or complements to synthetic NSAID-based topical therapies.

CONCLUSION

This study successfully formulated and characterized a stable topical ointment containing ethanolic extract of *Zingiber officinale* var. rubrum (red ginger) as a phytopharmaceutical anti-inflammatory preparation. The formulations exhibited consistent physicochemical stability, optimal pH within the physiological skin range, and satisfactory spreadability and adhesion, indicating suitability for dermal application. In vivo evaluation using the carrageenan-induced paw edema model demonstrated that the ointment exerted significant, dose-dependent anti-inflammatory activity, with the 15% w/w formulation showing efficacy comparable to diclofenac sodium ointment (1% w/w). These findings confirm that red ginger bioactives retain pharmacological potency when incorporated into a semisolid matrix.

The novelty of this work lies in establishing a direct correlation between the physical stability of a natural ointment system and its biological performance, providing a mechanistic basis for optimizing phytopharmaceutical formulations. This differs from previous studies that focused solely on extract activity without considering formulation integrity. Further investigations—such as permeation kinetics, stability under accelerated conditions, and molecular docking of active compounds—are recommended to support clinical translation and commercialization of red ginger ointment as a natural, safer alternative to topical NSAIDs.

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