

Antiinflammatory Potential of Red Ginger (*Zingiber officinale* var. *rubrum*) In Vivo

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ABSTRACT

Background: Red ginger (*Zingiber officinale* var. *rubrum*) contains bioactive phenolic compounds with anti-inflammatory properties, but data on its topical efficacy are limited. Objective: To evaluate the anti-inflammatory potential of topically applied red ginger ethanol extract in a carrageenan-induced paw edema model. Methods: Twenty-five male Swiss Webster mice were randomly assigned to five groups (n=5): negative control (1% CMC-Na), positive control (0.1% sodium diclofenac gel), and red ginger extract at 0.5%, 1%, and 1.5%. Inflammation was induced by intraplantar injection of 0.1 mL 1% carrageenan. Treatments were applied topically (0.1 mL spray) 30 minutes post-induction. Paw volume was measured using a digital plethysmometer at 30, 60, and 90 minutes post-treatment. Anti-inflammatory activity was assessed using Area Under the Curve (AUC) and Percentage of Anti-inflammatory Activity (%AIA). Results: The 1.5% extract showed the highest activity, with AUC values of 0.0410, 0.0245, and 0.0130 mL·hour at 30, 60, and 90 minutes, respectively. %AIA at 90 minutes reached 91.10%, approaching the positive control (94.86%). Significant differences were found between treatment groups and the negative control (p<0.05), with the 1.5% extract showing comparable efficacy to sodium diclofenac. Conclusion: Topical application of 1.5% red ginger ethanol extract exhibits potent anti-inflammatory activity comparable to 0.1% sodium diclofenac. Practical implication: Red ginger extract offers an affordable, accessible natural alternative for managing localized inflammation, particularly in resource-limited settings.

Keywords: red ginger, anti-inflammatory, *Zingiber officinale* var. *rubrum*, topical, AUC, %AIA

ABSTRAK

Latar belakang: Jahe merah (*Zingiber officinale* var. *rubrum*) mengandung senyawa fenolik bioaktif dengan sifat antiinflamasi, namun data tentang efektivitas topikalnya terbatas. Tujuan: Mengevaluasi potensi antiinflamasi ekstrak etanol jahe merah yang diaplikasikan secara topikal pada model edema kaki yang diinduksi karagenan. Metode: Dua puluh lima mencit jantan Swiss Webster dialokasikan secara acak ke dalam lima kelompok (n=5): kontrol negatif (CMC-Na 1%), kontrol positif (gel natrium diklofenak 0,1%), dan ekstrak jahe merah konsentrasi 0,5%; 1%; dan 1,5%. Inflamasi diinduksi dengan injeksi intraplantar karagenan 1% sebanyak 0,1 mL. Perlakuan diberikan secara topikal (semprot 0,1 mL) 30 menit pasca induksi. Volume edema diukur dengan plethysmometer digital pada 30, 60, dan 90 menit setelah perlakuan. Aktivitas antiinflamasi dinilai menggunakan Area Under the Curve (AUC) dan Persentase Daya Antiinflamasi (%DAI). Hasil: Ekstrak 1,5% menunjukkan aktivitas tertinggi dengan nilai AUC 0,0410; 0,0245; dan 0,0130 mL.jam masing-masing pada 30, 60, dan 90 menit. %DAI pada 90 menit mencapai 91,10%, mendekati kontrol positif (94,86%). Terdapat perbedaan signifikan antar kelompok dan kontrol negatif (p<0,05), dengan ekstrak 1,5% menunjukkan efektivitas sebanding natrium diklofenak. Kesimpulan: Aplikasi topikal ekstrak etanol jahe merah 1,5% memiliki aktivitas antiinflamasi kuat yang sebanding dengan natrium diklofenak 0,1%. Implikasi praktis: Ekstrak jahe merah dapat menjadi alternatif alami yang terjangkau dan mudah diakses untuk penanganan inflamasi lokal, terutama di daerah dengan sumber daya terbatas.

Kata kunci: jahe merah, antiinflamasi, *Zingiber officinale* var. *rubrum*, topikal, AUC, %DAI

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INTRODUCTION

Inflammation is a complex biological response triggered by infection, irritation, or tissue damage, characterized by classical signs such as redness (*rubor*), heat (*calor*), swelling (*tumor*), pain (*dolor*), and loss of function (*functio laesa*). This response serves as a protective mechanism aimed at eliminating harmful stimuli, clearing damaged cells, and initiating tissue repair. However, when excessive or unresolved, inflammation may contribute to chronic tissue damage and play a significant role in the pathogenesis of various degenerative, autoimmune, and cardiovascular diseases [1,2].

The primary pharmacological intervention for inflammation involves nonsteroidal anti-inflammatory drugs (NSAIDs), such as sodium diclofenac, ibuprofen, and aspirin. These drugs inhibit cyclooxygenase (COX) enzymes, particularly COX-2, thereby reducing the synthesis of pro-inflammatory prostaglandins [3]. Despite their effectiveness, prolonged systemic NSAID use is associated with gastrointestinal irritation, nephrotoxicity, and cardiovascular risks. Non-selective inhibition of the constitutive COX-1 isoform is closely linked to reduced synthesis of cytoprotective prostaglandins in the gastric mucosa, leading to ulcers and bleeding [4,5]. These limitations have driven interest in safer, natural alternatives, especially via topical administration that minimizes systemic exposure [6].

Indonesia, as one of the world's most biodiverse countries, possesses a wealth of medicinal plants. Among them, red ginger (*Zingiber officinale* var. *rubrum*) is notable for its high content of bioactive compounds such as gingerol, shogaol, zingerone, and essential oils [7,8]. Compared to other ginger varieties, red ginger has a higher essential oil content (2.58-2.72%) and a concentrated oleoresin rich in phenolic compounds [9]. Studies have confirmed that 6-gingerol and 6-shogaol

are the major bioactive constituents responsible for its potent anti-inflammatory, analgesic, and antioxidant activities [10]. The anti-inflammatory mechanism of red ginger involves inhibition of prostaglandin synthesis, downregulation of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6), and modulation of key pathways such as NF- κ B and MAPK [7,11].

Previous studies have demonstrated that red ginger extract reduces eosinophil counts in asthmatic rats and prevents protein denaturation, indicating its anti-inflammatory potential [12,13]. Recent research also showed that red ginger ointment formulations exhibit dose-dependent anti-inflammatory activity [14]. However, data on its *in vivo* efficacy via the topical route, especially using quantitative parameters such as Area Under the Curve (AUC) and Percentage of Anti-inflammatory Activity (%AIA), remain limited. AUC provides a cumulative representation of the inflammatory response over time, offering a more accurate estimate of the anti-inflammatory profile [15].

Therefore, this study aimed to comprehensively evaluate the anti-inflammatory potential of topically applied red ginger ethanol extract in a carrageenan-induced acute inflammation model and to identify the optimal concentration that exhibits efficacy comparable to 0.1% sodium diclofenac.

MATERIALS AND METHODS

Study Design

This study used a laboratory-based experimental design with a post-test only control group model. The carrageenan-induced paw edema method was employed to assess anti-inflammatory activity [15].

Experimental Animals

Twenty-five male Swiss Webster mice (*Mus musculus*), aged 2-3 months and weighing 20-25 g, were obtained from the certified animal facility of Institut Teknologi dan Kesehatan Bintang

Persada. Inclusion criteria were healthy animals with no signs of illness or injury. Exclusion criteria included abnormal behavior, weight loss exceeding 10% during acclimatization, or signs of infection at the injection site. Sample size was determined using the Federer formula: $(n-1)(t-1) \geq 15$, with $t = 5$ groups, giving $n \geq 5$, thus a total of 25 mice. Animals were acclimatized for 7 days under standard conditions (12-h light/dark cycle, $25 \pm 2^\circ\text{C}$, 50-60% humidity) with free access to standard pellet food and water *ad libitum* [16].

Randomization and Blinding

Mice were randomly assigned to five groups ($n=5$ each) using a simple random number table. To minimize bias, the researcher performing paw volume measurements was blinded to group allocation. Treatments were prepared and labeled by a separate researcher not involved in data collection.

Plant Material and Extraction

Fresh red ginger rhizomes (*Zingiber officinale* var. *rubrum*) were obtained from a traditional market in Denpasar, Bali, and authenticated at the Herbarium Laboratory, Udayana University (voucher specimen No. 123/UN14.2.2/2025). The rhizomes were washed, thinly sliced, and dried in an oven at 40°C for 48 h until constant weight (dry weight 450 g from 2 kg fresh material, yield 22.5%). The dried material was ground into a coarse powder. Maceration was performed by soaking 450 g of powder in 2.25 L of 96% ethanol at room temperature for 3×24 h, with solvent replacement every 24 h. The combined macerate was filtered and concentrated using a rotary evaporator (Buchi R-300) at 40°C under reduced pressure to obtain a thick extract (45 g, yield 10% w/w) [17,18]. The extract was stored in a desiccator and later diluted in sterile distilled water to prepare topical spray formulations at concentrations of 0.5%, 1%, and 1.5% (w/v).

Treatment Groups and Induction

Mice were randomly divided into five groups ($n=5$ each):

- Group I (negative control): 1% CMC-Na
- Group II (positive control): 0.1% topical sodium diclofenac gel
- Group III: 0.5% red ginger extract
- Group IV: 1% red ginger extract
- Group V: 1.5% red ginger extract

Acute inflammation was induced by intraplantar injection of 0.1 mL of 1% carrageenan into the right hind paw. Thirty minutes after induction, treatments were applied topically by spraying 0.1 mL onto the inflamed plantar surface. Paw edema volume was measured using a digital plethysmometer (Ugo Basile 7140) at 30, 60, and 90 minutes post-treatment. Each measurement was performed in triplicate and the average was recorded.

Data Analysis

The anti-inflammatory response was evaluated using the Area Under the Curve (AUC), calculated by the trapezoidal rule:

$$AUC_n = \frac{(V_{i-1})}{2} \times t$$

where V_i is the paw volume at the i -th measurement (mL), V_{i-1} is the volume at the previous measurement (mL), and t is the time interval (hours). The Percentage of Anti-inflammatory Activity (%AIA) was calculated as:

$$\%AIA = \frac{AUC \text{ negative control} - AUC \text{ treatment}}{AUC \text{ negative control}} \times 100\%$$

This formula compares the cumulative inflammatory response of a treatment group to that of the negative control. A higher %AIA indicates greater reduction in inflammation, with 0% representing no effect and 100% representing complete inhibition [15]. Statistical analysis was performed using SPSS version 26.0. Normality was tested with the Shapiro-Wilk test, and homogeneity of variances with Levene's test. Normally distributed and homogeneous data were analyzed by one-way ANOVA followed by Tukey's

HSD post-hoc test. Non-normally distributed or heterogeneous data were analyzed by the Kruskal-Wallis test. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS

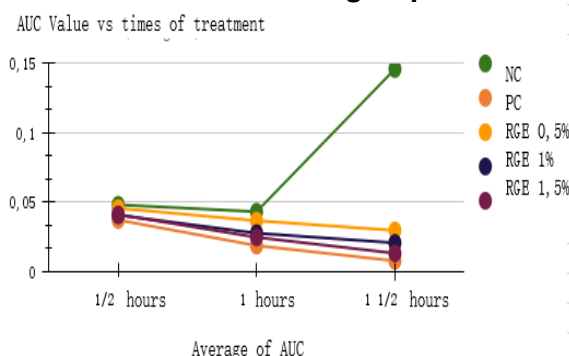
Paw Edema Volume and AUC

Red ginger extract exhibited dose- and time-dependent anti-inflammatory activity. The negative control group showed a progressive increase in paw edema, reflecting a strong inflammatory response. In contrast, the positive control and all red ginger extract groups showed varying degrees of edema reduction, with the 1.5% extract showing the most substantial decrease (Table 1). Figure 1 presents the comparative AUC values across treatment groups.

Table 1. Mean Area Under the Curve (AUC) Values (mL·hour)

Treatment Group	AUC 30 min	AUC 60 min	AUC 90 min
Negative Control (1% CMC-Na)	0.0480	0.0430	0.1460
Positive Control (0.1% Na diclofenac)	0.0370	0.0185	0.0075
Red Ginger Extract 0.5%	0.0455	0.0365	0.0295
Red Ginger Extract 1%	0.0405	0.0275	0.0205
Red Ginger Extract 1.5%	0.0410	0.0245	0.0130

Figure 1. Area Under the Curve (AUC) values across treatment groups.



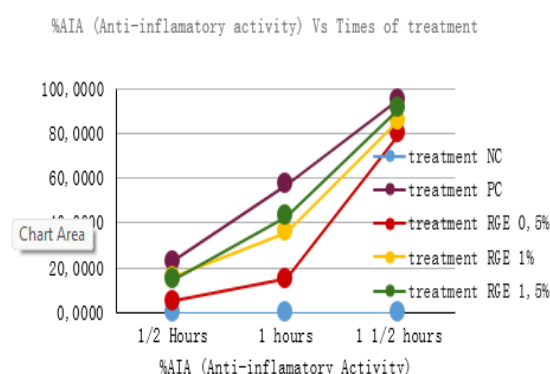
Percentage of Anti-inflammatory Activity (%AIA)

The %AIA values increased with both concentration and time. At 90 minutes, the 1.5% extract achieved 91.10%, closely approaching the positive control (94.86%) (Table 2). Figure 2 illustrates the anti-inflammatory activity percentages.

Table 2. Percentage of Anti-inflammatory Activity (%AIA)

Treatment Group	%AIA 30 min	%AIA 60 min	%AIA 90 min
Negative Control (1% CMC-Na)	0.0000	0.0000	0.0000
Positive Control (0.1% Na diclofenac)	22.9167	56.9767	94.8630
Red Ginger Extract 0.5%	5.2083	15.1163	79.7945
Red Ginger Extract 1%	15.6250	36.0465	85.9589
Red Ginger Extract 1.5%	14.5833	43.0233	91.0959

Figure 2. Percentage of Anti-inflammatory Activity (%AIA) across treatment groups.



Statistical Analysis

The Shapiro-Wilk test indicated normal distribution at 30 minutes ($p > 0.05$) but not at 60 and 90 minutes ($p < 0.05$). Levene's test showed homogeneity at 30 minutes ($p = 0.586$) but heterogeneity at 60 minutes ($p = 0.023$) and 90 minutes ($p < 0.001$). One-way ANOVA at 30 minutes revealed a significant difference among groups ($F(4,20) = 4.427$, $p = 0.010$). Kruskal-Wallis tests at 60 and 90 minutes also showed significant differences ($p < 0.001$). Tukey's HSD

post-hoc analysis placed the 1.5% red ginger extract and the positive control in the same homogeneous subset, indicating comparable efficacy.

DISCUSSION

The carrageenan-induced paw edema model is a well-established method for evaluating anti-inflammatory agents, characterized by a biphasic response: an initial phase (0-1 h) mediated by histamine and serotonin, followed by a secondary phase (1-3 h) driven by kinins and prostaglandins [15,19]. The significant reduction in paw volume and %AIA observed at 60 and 90 minutes in the 1.5% red ginger extract group indicates that the bioactive compounds effectively inhibit the cyclooxygenase (COX) pathway and subsequent prostaglandin synthesis.

The comparable efficacy of the 1.5% red ginger extract to 0.1% sodium diclofenac is particularly noteworthy. Sodium diclofenac is a potent synthetic NSAID that non-selectively inhibits COX-1 and COX-2, thereby reducing prostaglandin production [5]. Matching its effect with a natural extract highlights the therapeutic potential of red ginger. The likely mechanism involves multi-targeted inhibition by the synergistic action of various phytochemicals present in the extract, including gingerols, shogaols, and essential oils [7,8].

The anti-inflammatory mechanism of red ginger's bioactive compounds has been extensively investigated. Gingerol and shogaol have been shown to inhibit the expression of COX-2 and 5-lipoxygenase (5-LOX), key enzymes in the production of prostaglandins and leukotrienes [11,20]. At the transcriptional level, these compounds suppress the activation of nuclear factor kappa-B (NF- κ B), a master regulator of pro-inflammatory gene expression, thereby reducing the production of cytokines such as TNF- α , IL-1 β , and IL-6 [21,22]. Additionally, 6-shogaol inhibits leukocyte infiltration into inflamed tissues and reduces the expression of inducible nitric oxide synthase (iNOS),

decreasing nitric oxide production [23]. Recent *in silico* studies further suggest that ginger compounds have high binding affinity for Toll-like receptor 6 (TLR6), preventing the activation of innate immune responses [24].

Topical administration offers strategic advantages by allowing high local concentrations of active compounds at the inflammation site while minimizing systemic exposure, thus reducing the risk of gastrointestinal and cardiovascular side effects associated with oral NSAIDs [6,25]. The use of 96% ethanol as the vehicle likely enhances skin penetration by disrupting the lipid structure of the stratum corneum. Moreover, the natural essential oils present in red ginger extract (e.g., camphene, eugenol, zingiberene) may act as natural penetration enhancers [26,27]. Recent studies have also shown that ginger extract can be effectively delivered through the skin using lipid nanoparticles or transethosomes, further supporting its potential for topical use [26,27].

The time-dependent increase in %AIA from 14.58% at 30 minutes to 91.10% at 90 minutes for the 1.5% extract indicates that the active compounds require time to penetrate the skin barrier and reach target cells. This temporal profile aligns with the secondary phase of carrageenan-induced inflammation, which is dominated by prostaglandin synthesis and is the primary target of both NSAIDs and ginger-derived compounds [15,19].

These findings are consistent with previous studies. Palupi et al. reported that red ginger extract reduced eosinophil counts and mast cell degranulation in asthmatic rats [12]. Tukiran et al. demonstrated anti-inflammatory activity through inhibition of protein denaturation [13]. Fitri et al. showed that a 15% red ginger ointment achieved 60.8% inhibition comparable to diclofenac [14]. The present study extends these findings by showing that a 1.5% topical red ginger extract achieves

91.10% inhibition, which is statistically equivalent to 0.1% sodium diclofenac. This study has several limitations. The observation period was limited to 90 minutes, which captures the acute phase but does not provide information on the duration of action or the resolution phase. Additionally, direct measurement of pro-inflammatory mediators (e.g., PGE2, TNF- α , IL-1 β) in paw tissue would provide more definitive evidence of the underlying mechanism [28].

CONCLUSION

Topically applied ethanol extract of red ginger (*Zingiber officinale* var. *rubrum*) exhibits significant anti-inflammatory activity in a carrageenan-induced acute inflammation model. The 1.5% concentration demonstrated the most potent effect, achieving 91.10% inhibition at 90 minutes, which is statistically and clinically comparable to 0.1% sodium diclofenac. The anti-inflammatory efficacy was time- and dose-dependent, with the most pronounced effects observed during the secondary phase of inflammation, consistent with inhibition of prostaglandin synthesis. These findings support the development of red ginger as a natural, safe, and effective topical anti-inflammatory agent, offering a promising alternative for managing localized inflammation.

Recommendations for future research: Extended observation periods (up to 6-12 hours) should be employed to evaluate the duration of action and resolution phase. Direct quantification of pro-inflammatory mediators (PGE2, TNF- α , IL-1 β) in paw tissue is recommended to confirm the molecular mechanism. Furthermore, formulation optimization using nanotechnology (e.g., nanostructured lipid carriers, transethosomes) could enhance transdermal delivery and prolong the therapeutic effect, facilitating clinical translation of red ginger-based topical products.

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