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Rheological and Pharmacological Evaluation of High-Strength *Zingiber officinale* Topical Ointments for Antinociceptive and Anti-Inflammatory Effects

A. J. OLUSOLA[1,B,C,D,E] A.O. AWOLESI [2,B,C,D,E] O.A. ADELEYE [3,A,B,C,D,E,F]
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[1]*Department of Pharmacology and Toxicology, Federal University Oye-Ekiti, Ekiti State, Nigeria.*
[2]*Department of Pharmacognosy and Herbal Medicine, Federal University Oye-Ekiti, Ekiti State, Nigeria.*
[3]*Department of Pharmaceutics and Pharmaceutical Technology, Federal University Oye-Ekiti, Ekiti State, Nigeria.*

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article.

Abstract

Background: *Zingiber officinale* (ZO) is known for its pain-relieving and anti-inflammatory properties, but high-concentration topical formulations have not been well studied. This study evaluates how high extract loading affects rheological behavior and pharmacological activity.

Objectives: This study formulated ZO ointments with varying high concentrations and evaluated the impact of composition on rheological properties, antinociceptive, and anti-inflammatory efficacy in Wistar rats.

Materials and Methods: Dried ginger rhizomes were macerated in ethanol, and the extract was incorporated into ointment bases at 51.28% (formulation A), 41.03% (formulation B), and 30.77% (formulation C) w/w. Formulations were tested for physicochemical properties and efficacy using the hot-plate paw-lick and egg albumin-induced paw oedema assays. Rats received vehicle, methyl salicylate, or ZO extract (ZOE) ointments.

Results: Higher extract concentrations had better ointment spreadability and appearance. All formulations showed pseudoplastic flow, with viscosity inversely related to extract content. ZOE ointments produced dose-dependent antinociceptive and anti-inflammatory effects, with formulation A having the most significant effects.

Conclusion: Incorporating high concentrations of ZOE into topical ointments significantly enhanced both antinociceptive and anti-inflammatory efficacy. Formulation A provided the optimal balance of superior pharmacological activity and desirable physical properties. These findings indicate that ZOE ointments with higher concentrations have the potential to relieve localized pain and inflammation.

Keywords: *Zingiber officinale*; antinociceptive; anti-inflammatory; ointment

INTRODUCTION

Pain and inflammation are common in nearly all diseases (Viderman et al., 2023; Yacine et al., 2025). Systemic treatments are effective but may cause systemic side effects. Accordingly, there is a continued need for safer alternatives. Topical formulations have the advantage of targeting therapy directly to pain and inflammation sites with limited systemic absorption (Zhao et al., 2024). Pharmaceuticals derived from herbal extracts, if formulated for topical use, will provide complementary or alternative treatments (Adeleye et al., 2019; Ajala et al., 2020). This approach increases local drug concentration, systemic exposure, decreases toxicity, and improves patient compliance by bypassing the gastrointestinal tract and hepatic first-pass metabolism (Zhao et al., 2024).

Zingiber officinale (ZO), commonly known as ginger, is widely distributed (Ayustaningwarno et al., 2024; Mao et al., 2019). Ginger has applications in traditional medicine for stomach symptoms, nausea, pain, and swelling, as well as for liver protection (Mao et al., 2019). Its primary active constituents include gingerols, shogaols, and anthocyanins, which possess remarkable antioxidant, anti-inflammatory, and analgesic activities (Broeckel et al., 2025; Pázmándi et al., 2024). These could inhibit enzymes related to inflammation (Ballester et al., 2023). Ginger may help reduce pain and swelling in ways similar to some common pain relievers (Gurung et al., 2022; Pakale et al., 2024).

Despite the recognized bioactivity of ginger, the effectiveness of its compounds in dermal or transdermal applications is often limited by delivery challenges (Hassan et al., 2023). Many commonly used topical ginger formulations rely on low extract concentrations that do not reach an effective level. One example is a ginger ointment tested at 0.05%, which provided some relief but did not show a clear difference from a placebo for episiotomy discomfort (Cheshfar et al., 2023). In another case, low concentrations of 0.025%-0.05% were effective in certain inflammation models but increasing the concentration to 1%–5% resulted in a loss of anesthetic activity (Kravchenko et al., 2019). These indicate inconsistencies in determining the optimal dose. Furthermore, there is a paucity of information regarding the effects and efficacy of high extract concentrations, highlighting the need for further investigation in this area.

In this study, we hypothesized that systematically testing ointments with high ZOE loads would be crucial to determine the effectiveness of high extract load, elucidate whether antinociceptive and anti-inflammatory effects follow the same concentration-response relationship, and understand how high extract loading influences critical formulation properties like rheology and stability. Therefore, the present study formulates ZOE into a conventional ointment base at relatively high extract loads (30.77–51.28% w/w) and evaluates the interplay between formulation composition and topical pharmacological performance. By correlating viscosity, extract concentration, and therapeutic response, this work provides new formulation-driven insights into optimizing topical herbal analgesic and anti-inflammatory preparations, which have not been adequately addressed in previous studies.

MATERIALS AND METHOD

Plant Material and Extraction

Fresh rhizomes of ZO were purchased from a local market in Shagamu and authenticated at The Forest Herbarium Ibadan (FHI), Forest Research Institute of Nigeria (FRIN), Ibadan (voucher number: FHI 107935). The rhizomes were washed, sliced, and dried in the shade. Dried material (500 g) was pulverized and macerated in 95% ethanol for 72 hours with intermittent shaking. The ZO extract (ZOE) was filtered and concentrated under reduced pressure. The ZOE was dried to make a solid mass. The dry ZOE weighed 93.31 g, and the extractive yield was 18.7% w/w. The ZOE was stored in a desiccator until it was formulated for use.

Ointment Formulation

The ointment base was prepared following the British Pharmaceutical Codex (BPC) formula. Wool fat and white beeswax formed the oleaginous phase, with a small amount of water added to facilitate emulsification. To enhance skin penetration and produce a cooling effect, menthol and castor oil were included. ZOE was subsequently incorporated into the base at three concentrations (51.28%, 41.03%, and 30.77% w/w). The composition of the resulting formulations, each prepared in batches of about 48.75 g, is detailed in Table 1. After preparation, the ointments were transferred into amber glass jars and stored at room temperature. A reference standard ointment (Neurogesic®) containing methyl salicylate and menthol in a similar base was obtained and used as a positive control in biological tests. An empty base containing menthol, but no active ginger or methyl salicylate was also prepared as a negative control.

Table 1. Composition of ZOE ointment formulations

Ingredient	A	B	C
ZOE (g)	25.0	20.0	15.0
Wool fat (anhydrous lanolin) (g)	5.25	10.25	15.25
White beeswax (g)	10.0	10.0	10.0
Menthol (g)	5.0	5.0	5.0
Castor oil (g)	1.25	1.25	1.25
Distilled water (g)	2.25	2.25	2.25
Total batch weight (g)	48.75	48.75	48.75

A = 51.28% ZOE, B = 41.03% ZOE, C = 30.77% w/w ZOE.

Physical and Chemical Evaluation of Ointments

The ZOE ointments were evaluated for organoleptic and physicochemical properties. Color and homogeneity were visually assessed against a white background under natural light. Odor was characterized by direct sniffing. Texture, spreadability, and greasiness were determined by applying approximately 0.5 g of ointment between the thumb and index finger and spreading it on a glass plate. Spreadability was classified as easy, moderate, or difficult based on the effort required to achieve an even film. Viscosity and rheological behavior were measured using a Brookfield rotational viscometer (Model DV2T,

Brookfield Engineering Laboratories, USA) at 26 °C (±1 °C) with spindle #7. Measurements were performed at increasing shear rates from 5 to 100 rpm, with a 30-second equilibration time at each speed. Both viscosity (in centipoise, cP) and torque (in percent) were recorded. Stability was monitored under ambient storage conditions (25–30 °C) for four weeks, with weekly visual inspections for phase separation, precipitation, or changes in color, odor, and consistency.

Phytochemical Screening

Preliminary phytochemical tests were conducted on the ginger ethanol extract to identify major classes of secondary metabolites, using standard qualitative methods (Pandey & Tripathi, 2014; Shaikh & Patil, 2020) Tests included Mayer's reagent for alkaloids, Molisch's test for carbohydrates, alkaline reagent test for flavonoids, Borntrager's test for anthraquinone glycosides, froth test for saponins, ferric chloride test for tannins (phenolics), and Ninhydrin test for amino acids/proteins, among others (Kancherla et al., 2019). The appearance of characteristic color changes or precipitates in these assays indicated the presence or absence of each phytochemical group.

Experimental Animals and Groupings

Adult Wistar rats (either sex, 150 – 180 g) were obtained from the faculty's animal facility. They were housed under standard laboratory conditions (a 12-h light/12-h dark cycle, ~25°C) with free access to food and water. The rats were acclimatized for one week before the experiments. All animal procedures were carried out in accordance with international guidelines for the care and use of laboratory animals. Efforts were made to minimize animal suffering and to use the minimum number of animals necessary to achieve statistical significance.

For each assay, Rats were randomly divided into five groups of five animals each (n = 5):

- Group A: ZOE ointment 51.28% w/w.
- Group B: ZOE ointment 41.03% w/w.
- Group C: ZOE ointment 30.77% w/w.
- Group D: Positive control, treated with standard methyl salicylate ointment (Neurogesic®) applied topically.
- Group E: Negative control (vehicle only).

To minimize observer bias, the experimenter recording behavioral responses (e.g., latency, paw circumference) was blinded to the treatment group assignments.

Antinociceptive Activity

The hot-plate test was used to evaluate the antinociceptive effect of the ZO extract ointment (Deuis et al., 2017). For treatment, approximately 0.5 g of the assigned ointment was applied to each rat. The ointment was rubbed onto the plantar surface of both hind paws up to the ankle joint. Rats were then kept for 30 minutes to allow dermal absorption of the active constituents. After this pre-treatment period, each rat was individually placed on a hot-plate analgesia meter (Orchid Scientific, model HC-01) to perform the hot-plate paw-lick test. A Plexiglas cylinder was used to confine the rat on the plate. The latency (reaction time) to the pain response, measured as the time (in seconds) until the rat began licking one hind paw or attempted to jump, was recorded with a stopwatch. To avoid tissue damage, a cutoff time of 60 s was imposed; any rat not responding by 60 s was removed to prevent injury (and assigned 60 s as latency). Each animal's paw-lick latency was measured at three time points: thirty minutes, one hour, and two hours after ointment application (corresponding to 0, 30, and 90 min after the hot-plate test initiation). The hot-plate surface was wiped clean between trials. Latency measurements were averaged within each group (5 rats per time point). An increase in pain reaction time (latency) compared to the negative control indicates an antinociceptive effect. After testing, rats were observed for full recovery, and no injuries were noted.

Anti-Inflammatory Activity Test

The anti-inflammatory effect of the ZOE ointments was assessed using the acute hind-paw oedema model induced by egg albumin. The ointments were applied to the hind paws 30 minutes before inflammation induction, in the same manner as described above for the antinociceptive test (rubbing on the paw and lower leg, then waiting 30 min). To induce oedema, 0.1 mL of fresh egg albumin was injected subcutaneously into the plantar tissue of the left hind paw of each rat (intradermal plantar injection). Paw circumference (in cm) was measured at specific time intervals as an index of oedema size. A piece of flexible thread was placed around the widest part of the paw (metatarsal area), and the length of the thread was then measured on a ruler to determine the circumference (Deuis et al., 2017). Measurements were taken at 1, 2, 3, and 4 h after the albumin injection. For consistency, the same researcher performed all measurements, and care was taken to mark the paw at the same position each time to ensure accurate measurements. Mean paw circumference for each group was calculated at each time point. The change in paw circumference from 1 hour to 4 hours was used to quantify the anti-inflammatory effect (a greater reduction in swelling indicates better activity).

Data and Statistical Analysis

Data are expressed as mean ± standard error of the mean (SEM). Differences between groups were analyzed using analysis of variance (ANOVA), followed by Dunnett's multiple-comparison test to compare each treatment group with the control group, using GraphPad Prism 8 (GraphPad Software, San Diego, CA). A p-value of < 0.05 was considered statistically significant.

RESULTS

Phytochemical Constituents of ZOE

Phytochemical screening confirmed the presence of carbohydrates, flavonoids, glycosides, saponins, triterpenoids/steroids, and alkaloids (Table 2).

Table 2. Phytochemical screening of *Zingiber officinale* ethanol extract using standard qualitative tests.

Test (Reagent/Method)	Compound Class	Observation/Result	Outcome
Molisch's test	Carbohydrates	Purple ring at the interface	Positive
Alkaline reagent test	Flavonoids	Yellow coloration, decolorized with acid	Positive
Borntrager's test	Glycosides	Red coloration observed	Positive
Frothing test	Saponins	Persistent frothing	Positive
Salkowski's test	Triterpenoids/steroids	Golden-yellow coloration	Positive
Mayer's reagent	Alkaloids	Formation of precipitate	Positive

Ointment Physical Characteristics

All ZOE ointments were brown with a mentholated odor. Formulations A and B were dark brown, smooth, and spread easily, with a cooling effect. In contrast, formulation C was lighter, thicker, and grittier due to its higher wax content, making it harder to spread and wash off. All remained stable without phase separation and did not cause visible skin irritation in rats during the study period. Formulation A was most cosmetically elegant, whereas formulation C had poorer handling properties.

Rheological behavior

The viscosity and torque of the three ZOE ointment formulations were measured across a range of shear rates (5–100 rpm). The data is presented in Table 3. All formulations exhibited characteristic pseudoplastic (shear-thinning) behavior, with viscosity decreasing as the shear rate increased (Table 3). Formulation C (30.77% w/w ZOE) was the most viscous across all measured shear rates, followed by formulation B and then formulation A. For instance, at 5 rpm, the viscosity of formulation C was approximately 4.3 times greater than that of formulation A. Despite these differences, all formulations demonstrated sufficient viscosity for topical application without runoff.

Table 3. Rheological properties of ZOE ointment formulations at increasing shear rates.

SPINDLE NUMBER	RPM	VISCOSITY (centipoise)			TORQUE (%)		
		FORMULATION					
		A	B	C	A	B	C
7	5	18400	44000	80000	2.4	5.5	10.0
7	10	4600	25200	40000	1.2	6.5	10..1
7	20	4000	14200	23200	2.0	7.1	11.3
7	50	1400	6000	8640	1.5	7.5	11.6
7	100	920	3880	6000	2.2	9.7	14.3

Antinociceptive Effect in the Hot-Plate Test

The antinociceptive activity over time for all treatment groups is shown in Figure 1. The ZOE ointment formulations demonstrated significant, dose-dependent antinociceptive activity compared to the negative control. Following the application, all ZOE formulations (A, B, and C) and the positive control showed a significant increase in latency at 0.5 h ($p < 0.001$). The peak effect in all treated groups occurred at 0.5 h, with formulation A showing the highest mean latency (26.8 s), which was not statistically different from that of the positive control (25.8 s; $P > 0.05$). The antinociceptive effect gradually declined over time; however, all formulations maintained significantly higher latency than the negative control at 1 h ($P < 0.01$). By 2 h, only formulation A (51.28% w/w ZOE) retained a statistically significant antinociceptive effect ($P < 0.05$) compared to the negative control.

Anti-Inflammatory Effect in the Paw Oedema Test

The inhibitory effect of the topical ZOE formulations on egg albumin-induced paw edema over 4 hours is summarized in Table 4. ZOE ointments caused a significant reduction in acute hind-paw oedema induced by egg albumin. During the initial 3 h post-induction, paw circumference was significantly reduced in all treatment groups (Formulations A, B, and C) and the positive control compared with vehicle-treated animals ($P < 0.05$), indicating similar anti-inflammatory efficacy

across the treatments. At the 4 h interval, only animals treated with formulation A showed reductions in oedema compared with the vehicle ($P < 0.05$).

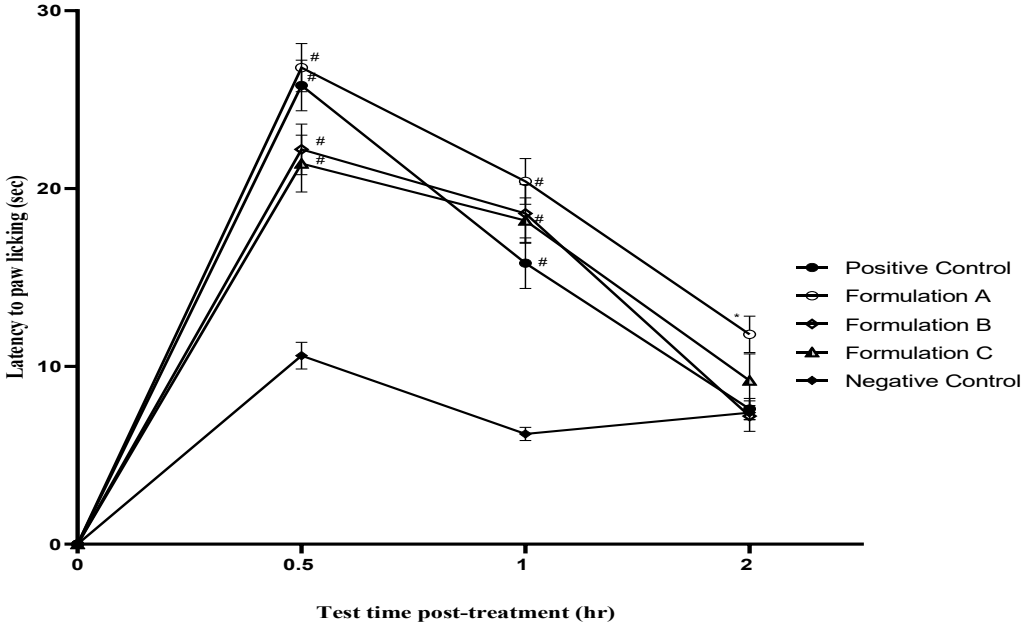

Figure 1: Antinociceptive activity (Paw-licking latency (seconds) of rats treated with ZOE ointments at varying concentrations. Values are expressed as mean ± SEM (n = 5). Two-way repeated-measures ANOVA and Tukey's multiple comparison test (* = $p < 0.05$, # = $p < 0.0005$ vs Negative control).

Table 4. Effect of topical ginger ointment formulations on mean paw circumference in the acute egg-albumin-induced inflammation model.

	Test Time Post-Treatment (h)			
Treatment Groups	**1 h**	**2 h**	**3 h**	**4 h**
Negative Control	2.9 ± 0.06	2.74 ± 0.08	2.54 ± 0.05	2.18 ± 0.04
Positive Control	2.48 ± 0.07*	2.24 ± 0.05**	2.12 ± 0.02**	2.04 ± 0.07
Formulation A	2.36 ± 0.05**	2.1 ± 0.04**	2 ± 0.04***	1.94 ± 0.05*
Formulation B	2.38 ± 0.09**	2.3 ± 0.07*	2.14 ± 0.04**	2.02 ± 0.04
Formulation C	2.52 ± 0.04**	2.36 ± 0.05*	2.22 ± 0.04**	2.08 ± 0.04

Values are expressed as mean ± SEM (n = 5). One-Way Repeated Measures ANOVA and Tukey's multiple comparison test (* = $p < 0.05$, ** = $p < 0.01$, and *** = $p < 0.001$ vs Negative control).

DISCUSSION

This study shows that formulating ZOE into high-concentration topical ointments produces significant, dose-dependent antinociceptive and anti-inflammatory activity, with formulation A providing the most sustained effect. These results suggest that high-strength preparations may address the limitations of traditional low-concentration topical ginger products by probably delivering enough bioactive constituents to the site of action for a robust effect. The finding that formulation A also had the lowest viscosity and best spreadability suggests that high extract loading may enhance both pharmacological efficacy and physical handling properties.

Both antinociceptive effects and reductions in edema were observed in this study, consistent with previous findings on the biological activity of ginger rhizomes. In the hot-plate test, ZOE ointments produced dose-

dependent antinociceptive effects, similar to results reported by Ojewole (2006). Likewise, the reduction of acute inflammation in the egg albumin-induced paw edema assay aligns with the observations of Bouchama et al. (2023) and Penna et al. (2003). Similarly, our findings align with observations from advanced delivery systems, such as the 5% ginger nanostructure lipid carriers reported by Amorndoljai et al. (2017) and the transethosomes reported by Hassan et al. (2023). Both studies highlight that getting enough active ingredients to the affected area is key for effects similar to synthetic NSAIDs such as diclofenac. However, Cheshfar et al. (2023) tested a 0.05% ginger ointment and observed only clinical improvements in episiotomy pain, which were not statistically significant. In contrast, our high-strength formulations produced clear statistical differences from controls, likely due to the much higher concentration used.

It should be noted that the extract loads used in this study (30.77–51.28% w/w) were chosen, in part, to make preclinical efficacy easier to observe and to evaluate the limits of conventional ointment bases. These concentrations are much higher than what would likely be practical for human use. The primary aim is to show that marked antinociceptive and anti-inflammatory effects are possible when the skin receives sufficient bioactive compounds.

Study Limitations

For clinical application, further work will likely need to focus on strategies to significantly lower the required dose through improved formulation. Also, the lack of long-term stability testing and mechanistic exploration should be addressed. Additionally, this study did not quantify individual bioactive constituents, such as gingerols, in the ointment formulations. Future studies should incorporate phytochemical profiling to better elucidate the relationship between compound levels and pharmacological effects.

CONCLUSION

Overall, this study shows that topical ZOE ointments, particularly at higher concentrations, exert clear dose-dependent antinociceptive and anti-inflammatory effects in preclinical models. Importantly, the findings point to a close interplay between formulation composition, rheological behaviour, and therapeutic performance. Among the tested formulations, Formulation A (51.28% w/w ZOE) emerged as the most effective, combining a high extract load with lower viscosity and improved spreadability. These findings emphasize that both the extract concentration and the formulation's rheological properties may interact to determine overall efficacy. To support clinical translation, future studies should prioritize formulation optimization to substantially lower the effective dose required.

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*Address for correspondence: Ayobami J. Olusola

Department of Pharmacology and Toxicology, Federal University Oye-Ekiti, Ekiti State, Nigeria.

Telephone: +2348069635222
E-mail: ayobami.olusola@fuoye.edu.ng
ORCID ID: 0000-0001-9781-4243

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