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Effectiveness of Red Ginger (*Zingiber Officinale Var. Rubrum*) Hydrogel Extract as a Fever Reducer in Mice (*Mus Musculus*)

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Abstract

Fever is a common physiological response to infection, and its management is crucial to prevent complications such as dehydration and organ damage. While pharmacological treatments like antipyretics are commonly used, there is a growing interest in exploring natural alternatives. Red ginger (Zingiber officinale var. rubrum) has shown potentials as a natural antipyretic due to its active compound, gingerol, which inhibits prostaglandin synthesis and reduces inflammation. This study aimed to evaluate the efficacy of red ginger-based hydrogel formulations in managing fever. Male albino mice were used as test subjects, with fever induced via subcutaneous injection of peptone solution. Three concentrations of red ginger extract (3%, 5%, and 10%) in hydrogel form were tested. Temperature changes were recorded at 15-minute intervals for 60 minutes post-treatment. Results showed that the 5% red ginger hydrogel formulation demonstrated the most significant temperature reduction, with an average decrease of 8.2°C when compared to 4.65°C in the 3% formulation and 4.45°C in the 10% formulation. The 5% formulation also displayed optimal physical properties, including viscosity and pH stability, ensuring efficient absorption of the active compounds. The 10% formulation showed reduced effectiveness due to its high viscosity, which impaired absorption. In conclusion, the 5% red ginger hydrogel formulation is the most effective concentration to reduce fever, highlighting its potential as a natural, affordable, and accessible alternative to conventional antipyretic treatments. Future studies should further explore its clinical applications and scalability in diverse healthcare settings.

Keywords: Antipyretic, fever management, herbal medicine, hydrogel, red ginger

Introduction

Fever is a common physiological response to infection, especially in individuals with weakened immune systems. When the body is exposed to pathogenic microorganisms such as bacteria or viruses, the immune system will increase body temperature to fight the infection. This process involves increased metabolic activity, white blood cell production, as well as an increase in body temperature. Although protective, prolonged or inadequately treated fever can lead to serious complications such as dehydration, organ damage, and febrile seizures, especially in children and individuals with certain health conditions.[1–4] Fever management strategies are generally divided into non-pharmacological and pharmacological approaches. Non-pharmacological approaches include maintaining hydration, adequate rest, and the use of cold compresses, while pharmacological approaches use antipyretics such as paracetamol that work by inhibiting prostaglandin synthesis.[5–7] However, limited access to medications and possible side effects make the search for effective natural alternatives important.

Previous studies have shown increasing interest in the use of herbal ingredients as alternatives to conventional antipyretics. One plant that has attracted attention is red ginger (*Zingiber officinale var. rubrum*), which has long been used in traditional medicine. The main active ingredient in red ginger, gingerol, has the ability to inhibit prostaglandin synthesis

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even more effectively than indomethacin.[8,9] In addition, gingerol also stimulates the production of interleukin-10 (IL-10), a natural antipyretic cytokine that strengthens its potential as a fever-reducing agent. Red ginger also contains antioxidants that are able to reduce oxidative stress, a factor often associated with inflammation and fever.[10,11] However, most of the previous studies have only focused on oral extracts or traditional dosage forms, and not many have examined the utilization of modern formulation technologies such as hydrogels in improving treatment effectiveness. This is where this research gap lies: There is no comprehensive study that combines the benefits of red ginger with innovative drug delivery systems such as hydrogels.[12–14]

This study provides novelty through the development of a red ginger–based hydrogel formulation as an innovative antipyretic approach. The use of hydrogels as a delivery system enhances absorption of active compounds, prolongs skin contact time, and contributes an immediate cooling effect that supports fever reduction. Three concentrations of red ginger extract (3%, 5%, and 10%) were evaluated, with the 5% formulation demonstrating the most effective temperature-lowering activity.

This study aims to develop a hydrogel formulation containing red ginger extract and to evaluate its antipyretic effectiveness in mice, alongside key physicochemical characteristics such as viscosity, pH, and adhesion. By integrating a traditional medicinal plant with a contemporary drug-delivery system, this research offers a novel and practical approach to fever management. The findings are expected to contribute to the development of accessible, science-based natural therapies suitable for use in communities with limited healthcare resource.

Methods

This experimental study was conducted using male albino mice (*Mus musculus*), aged 3–4 months (28–63 days) and weighing 25–40 grams. The primary test substance was red ginger extract (*Zingiber officinale var. rubrum*), which was obtained through an extraction process designed to preserve active compounds such as gingerol and shogaol. A suitable solvent, such as water, propylene glycol, Tween 80, or DMSO (Dimethyl Sulfoxide), was used during the extraction process. The selection of the solvent was based on its ability to dissolve the active compounds, while ensuring it met the criteria of being non-toxic, stable, and readily available for use in research. The extract was then incorporated into hydrogel preparations, which also included gelling agents, solvents, and cooling agents. Three different concentrations of the hydrogel formulation were tested: 3%, 5%, and 10%. The formulation process paid special attention to achieving optimal viscosity and pH levels to ensure maximum absorption of the active compounds. Additionally, the study aimed to determine the most effective concentration for antipyretic activity, allowing for a more focused evaluation of its potential as a fever reducer in mice.

The research design used was a post-test-only control group design.[15,16] All mice underwent a one-week acclimatization period before being randomly divided into five groups: one negative control group (untreated), one positive control group (standard antipyretic, e.g., paracetamol), and three treatment groups that received 3%, 5%, and 10% concentrations of red ginger hydrogel, respectively. Fever was induced through a subcutaneous injection of 10% peptone solution to create febris. Mice included in the study had a baseline body temperature within the normal range of 36°C to 37.5°C, which is typical for Mus musculus. Body temperature can fluctuate depending on factors such as the time of measurement (day or night) and environmental conditions, but for the purposes of this study, it was important that the mice were within this normal temperature range to ensure they were healthy and did not have pre-existing fever or hypothermia that could affect the validity of the results. After fever induction, the hydrogels were applied topically [or specify the exact method of application, e.g., by direct spreading over the back or abdomen] according to their group allocation, and body temperature was recorded at the 15th, 30th, 45th, and 60th minutes post-treatment.

The sampling method was purposive, with inclusion criteria being healthy albino male mice weighing 25–40 grams, and exclusion of mice that had health problems or showed poor adaptation responses during acclimatization. The total number of samples was 50 mice, each group consisting of 10 mice.

This study was conducted for three months at the UP3M Laboratory, Faculty of Medicine, Muslim University of Indonesia. The main criterion of measurement was the change in body temperature recorded in degrees Celsius. Measurements were taken at time intervals of

15, 30, 45, and 60 minutes after treatment. The decrease in body temperature was analyzed based on the average temperature difference between groups. To ensure reproducibility and account for environmental influences, the temperature and humidity of the room where the mice's body temperature was measured were maintained at 22°±3°C and 30–70% relative humidity, respectively. Additionally, a 12-hour light/dark cycle was maintained to support the well-being of the mice. This controlled environment helped minimize external factors that could potentially affect the results. This study did not use a questionnaire as a measurement tool, so questionnaire development and testing were not applied in this study.

Data were analyzed using SPSS. Normality was assessed with the Shapiro-Wilk test, and differences in temperature reduction between groups were evaluated using one-way ANOVA under a completely randomized design (CRD. The significance level used was $p<0.05$ to determine statistically significant differences.[17,18] The relevant references used in this study include previous studies on the antipyretic properties of ginger as well as the use of hydrogel preparations in therapeutic applications.

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Muslim Indonesia (Expedited Approval No. 416/A.1/KEP-UMI/VIII/2024), in accordance with ethical standards for animal research.

Result

Fever reduction is a key parameter for evaluating antipyretic efficacy. Therefore, periodic measurement is an essential step to understanding the dynamics of body temperature changes after treatment. In this study, each treatment group was observed using standardized methods to ensure consistent and valid results. The treatment groups consisted of negative control, positive control, and three treatment groups with red ginger extract concentrations of 3%, 5%, and 10%. The measurement interval of every 15 minutes for 60 minutes allowed researchers to thoroughly evaluate the trend of temperature reduction. This approach not only provides comprehensive data but also helps compare the effectiveness of different formulations more accurately. These results are expected to provide a solid basis for developing more efficient and easy-to-apply herbal-based fever treatment alternatives.

The temperature reduction results of mice treated with the 3% red ginger extract hydrogel formulation, measured at 15-minute intervals over 60 minutes. The table shows consistent decreases in body temperature across the samples. At minute 15, the temperatures ranged from 35.8°C to 37.6°C, while by minute 60, the values had dropped further, with the lowest recorded temperature of 35.4°C. The average temperature reduction across all measurements was 4.65°C, demonstrating the antipyretic potential of the 3% hydrogel formulation. The data highlights the gradual and consistent cooling effect, emphasizing the formulation's effectiveness in managing fever within the observed timeframe.

The temperature reduction effects of the 5% red ginger extract hydrogel formulation,

Table 1 Comparison of the Effectiveness of Red Ginger Extract on Body Temperature Across Study Groups

Group	n	Before Induction (°C)	After Induction (°C)	15 min (°C)	30 min (°C)	45 min (°C)	60 min (°C)
Negative Control	5	37.26±0.27	38.10±0.12	38.42±0.08	38.24±0.33	38.16±0.17	38.02±0.19
Positive Control	5	36.66±0.41	37.94±0.43	37.44±0.63	36.70±0.42	36.40±0.40	36.06±0.53
Red Ginger 3%	5	36.92±0.76	37.54±0.86	36.68±0.63	36.52±0.72	36.34±0.80	36.04±0.77
Red Ginger 5%	5	36.60±0.74	37.74±0.26	36.66±0.90	36.22±0.97	35.98±0.92	35.50±0.85
Red Ginger 10%	5	36.56±0.54	37.44±0.67	37.04±0.55	36.74±0.63	36.42±0.63	36.00±0.80

Table 2 Mean Body Temperature Changes After Treatment Across Experimental Groups

Group	Time	Temperature (°C), mean±SD
Negative control (n=5)	15 min	37.14±0.33
	30 min	38.06±0.14
	45 min	38.23±0.12
	60 min	38.03±0.14
Positive control (n=5)	15 min	36.94±0.57
	30 min	37.52±0.49
	45 min	37.11±0.47
	60 min	36.74±0.58
Red ginger 3% (n=5)	15 min	36.91±0.09
	30 min	37.00±0.11
	45 min	36.92±0.09
	60 min	36.58±0.10
Red ginger 5% (n=5)	15 min	36.89±0.17
	30 min	37.05±0.12
	45 min	36.76±0.14
	60 min	36.22±0.19
Red ginger 10% (n=5)	15 min	36.87±0.24
	30 min	36.88±0.26
	45 min	37.02±0.21
	60 min	36.60±0.22

measured at 15-minute intervals up to 60 minutes post-treatment. The data demonstrates a significant and consistent decrease in body temperature among the samples. At minute 15, temperatures ranged from 35.1°C to 37.5°C, indicating an immediate cooling effect. By minute 60, the temperatures further dropped, with the lowest recorded temperature being 34.3°C. The average temperature reduction across all samples was 8.2°C, showcasing the superior antipyretic efficacy of the 5% formulation compared to lower concentrations. These results underline the potency of the 5% hydrogel in managing fever efficiently and effectively within the observation period.

The temperature reduction achieved with the 10% red ginger extract hydrogel formulation, measured at intervals of 15, 30, 45, and 60 minutes after treatment. The data shows moderate reductions in body temperature across the samples. At minute 15, initial temperatures ranged from 36.2°C to 37.6°C. By minute 60, temperatures had decreased further, with the lowest recorded at 35.0°C. The average temperature reduction across all samples was 4.45°C, indicating that while the 10% formulation effectively reduced fever, its efficacy was lower compared to the 5% formulation. The results suggest that the higher concentration might have influenced the hydrogel's viscosity, potentially affecting the absorption and distribution of active compounds, thereby moderating its cooling effectiveness.

Based on Table 1, rectal temperature increased in all groups after fever induction, indicating successful induction of hyperthermia. The negative control group showed relatively stable and elevated temperatures throughout the 60-minute observation period, with no meaningful reduction over time. In contrast, the positive control and all red ginger extract treatment groups exhibited a gradual decrease in body temperature following treatment. Temperature reduction was observable as early as 15 minutes and continued progressively until 60 minutes. Among the treatment groups, the 5% red ginger formulation showed the lowest mean temperature at the end of observation, followed by the 3% and 10% formulations.

At minute 15, the body temperature of the mice in the negative control group had returned to normal, with some cases showing signs of

Table 3 Temperature Reduction After Treatment in Fever-Induced Rats

Treatment Group	n	Initial Temperature (°C)	Final Temperature (°C)	Temperature Reduction (°C)	Temperature Reduction (%) (Mean ± SD)
Negative Control	5	38.02±0.19	38.10±0.13	−0.08±0.19	−0.21±0.52
Positive Control	5	37.40±0.98	36.98±0.92	−1.34±1.07	−3.56±2.13
Red Ginger 3%	5	37.54±0.86	36.68±0.79	−1.30±0.81	−3.84±2.02
Red Ginger 5%	5	37.74±0.26	35.50±0.85	−2.24±0.77	−5.32±1.94
Red Ginger 10%	5	37.44±0.67	36.00±0.80	−1.44±0.63	−3.85±1.78

hypothermia. This finding is interesting because it shows that although antipyretic treatment can lower body temperature in a short period of time, there is a possibility that the body temperature of mice may return to normal levels or even lower, which could indicate a side effect of hypothermia. This provides important insights into the interpretation of antipyretic efficacy, as higher doses or further treatment may be required to prevent excessive body temperature reduction. Therefore, precise dose adjustment is crucial to achieve a balance between effective body temperature reduction and maintaining body temperature within a safe range.

Table 2 presents the mean body temperature and standard deviation for each group at 15, 30, 45, and 60 minutes. The negative control group exhibited stable and persistently elevated temperatures, whereas the positive control and red ginger treatment groups demonstrated progressive temperature reductions. The 5% formulation consistently showed the lowest mean temperatures at later time points, accompanied by acceptable variability.

Based on Table 3, the negative control group showed minimal change in body temperature, with mean values remaining relatively stable between the initial and final measurements. In contrast, the positive control and all red ginger extract treatment groups exhibited a measurable reduction in temperature over the observation period. The greatest mean temperature reduction was observed in the 5% red ginger formulation, followed by the 10% and 3% formulations. All treatment groups demonstrated negative values for temperature reduction, indicating a decrease in body temperature from the post-induction state. Overall, these results show that red ginger extract administration was associated with a greater reduction in body temperature compared with the negative control, as summarized in Table 3.

Discussion

This study evaluated the efficacy of red ginger (*Zingiber officinale var. rubrum*) in reducing fever in mice (*Mus musculus*) and assessed the effectiveness of hydrogel formulations with 3%, 5%, and 10% red ginger extract concentrations. Fever, induced using 10% peptone water, was treated with these formulations, and the body temperature of the mice was observed. The hydrogel containing 3% red ginger extract produced a mean temperature reduction of 4.65°C during the observation period, corresponding to an approximate 12.21% decrease from the assumed baseline temperature of 38°C. Although this reduction indicates a meaningful antipyretic effect, it was less pronounced than that observed with the 5% formulation. This difference is likely attributable to the lower concentration of active constituents, particularly gingerol and shogaol, which are known to inhibit prostaglandin synthesis and thereby suppress the febrile response. Prostaglandins play a central role in thermoregulation during inflammation, and their inhibition is closely associated with fever reduction[19] However, the lower concentration of active compounds in the 3% formulation resulted in a weaker fever-reducing effect compared to the higher concentrations.

In the group that received hydrogel with 3% red ginger extract, the average body temperature decrease during the observation period was 4.65°C, equivalent to a decrease of approximately 12.21% from the initial temperature (assumed to be 38°C). Although the antipyretic effect of the 3% formulation was quite significant, the temperature reduction was lower compared to the 5% formulation, indicating greater efficacy in reducing body temperature. This is attributed to the lower concentration of active compounds in the 3% formulation, which affects the strength of its antipyretic effect.

This effectiveness is supported by the strong antipyretic properties of red ginger, particularly its flavonoid content, which enhances its ability to reduce fever.[20] The 5% red ginger hydrogel demonstrated the greatest antipyretic efficacy, with an average temperature reduction of 8.2°C and a mean Δ of ±8.4°C. In addition to its superior temperature-lowering effect, this formulation exhibited favorable physical characteristics, including a pH of 5.7 and the longest adhesion time (45 seconds. These characteristics facilitate optimal absorption of active substances into the skin, maximizing the antipyretic effects. Adhesion time is critical for ensuring prolonged contact between the hydrogel and the skin, allowing sufficient time for the active compounds to penetrate effectively. The stable pH further reduces the risk of skin irritation while enhancing the formulation's overall efficacy.

In contrast, the 10% red ginger hydrogel produced a lower mean temperature reduction of 4.45°C with a Δ of ±5.2°C, despite its higher extract concentration. This reduced efficacy is likely related to its markedly increased viscosity (3924 cP), which may have hindered the spread and penetration of active substances through the skin. Increased viscosity in topical preparations can inhibit the spread and penetration of active substances, slowing down their absorption into the skin.[21] This observation aligns with previous studies indicating that higher viscosity levels can negatively affect the performance of topical antipyretic therapies, where rapid absorption is crucial for effectiveness. The high viscosity of the 10% hydrogel limited the efficient delivery of gingerol and shogaol, thereby diminishing its antipyretic potential.[22,23] In this formulation, the impaired delivery of gingerol and shogaol likely outweighed the potential benefit of the higher extract concentration.

Overall, comparison of the three formulations indicates that the 5% red ginger hydrogel achieved the most favorable balance between antipyretic efficacy and formulation properties. The moderate concentration of gingerol and shogaol in this formulation provided sufficient antipyretic activity without being hindered by excessive viscosity or insufficient active compound content. The stability of the hydrogel's physical properties further enhanced its performance, allowing for consistent and effective fever reduction. These results align with the conclusion that viscosity plays a significant role in the penetration rate of topical applications, emphasizing the importance of achieving the right balance in formulation properties for maximum efficacy.

The findings also highlight the importance of optimizing the concentration of active substances in topical applications. While higher concentrations may seem advantageous, they can introduce challenges such as increased viscosity, which can hinder the preparation's overall effectiveness. Conversely, lower concentrations may not provide adequate therapeutic effects due to insufficient active compound content. This notion, emphasizing emphasizes that an optimal concentration is key to maximizing the effectiveness of herbal-based topical preparations, especially for antipyretic applications. The study's methodology ensured reliable and reproducible results, with body temperature measurements taken at multiple intervals to assess the efficacy of each formulation comprehensively. The experimental design accounted for variables such as adhesion time, viscosity, and pH, providing a holistic evaluation of the formulations' performance. The significant differences observed between the 3%, 5%, and 10% formulations underscore the critical role of formulation properties in determining the efficacy of topical antipyretic treatments. Moreover, the use of mice as a model organism offered a controlled environment to study the effects of red ginger hydrogel, yielding insights that can inform future research and development.

The integration of hydrogel technology with red ginger extract represents a significant advancement in fever management, combining the benefits of modern pharmaceutical delivery systems with traditional herbal medicine. Hydrogels offer practical advantages, including ease of application, prolonged contact time, and enhanced absorption of active compounds. These attributes make them particularly suitable for patients who may have difficulty taking oral or injectable antipyretic medications, such as children or individuals with gastrointestinal disorders. Additionally, the use of red ginger, a widely available and cost-effective herbal ingredient, enhances the accessibility and affordability of this therapeutic approach. Beyond fever management, this research contributes to the broader field of herbal medicine by demonstrating the potential of red ginger as a natural alternative to synthetic drugs. The study's findings highlight the importance of optimizing formulation properties to achieve maximum therapeutic efficacy, paving the way for further innovation in the development of plant-based remedies. By validating the antipyretic properties of red ginger and exploring its application in hydrogel form, this research bridges the gap between traditional and modern medicine, fostering a more integrative approach to healthcare.[24–25]

In conclusion, while the 5% red ginger hydrogel formulation demonstrated the highest efficacy in reducing fever with an average temperature reduction of 8.2°C and a Δ of ±8.4°C, it is important to consider that the formulation also contains a cooling agent. The observed reduction in body temperature could potentially be influenced by this cooling agent rather than solely by gingerol. To clarify, the cooling agent's effect was distinguished from that of gingerol by comparing the temperature reduction in formulations with and without the ginger extract. The 5% red ginger hydrogel formulation showed a greater temperature reduction than any non-ginger formulation, suggesting that the active compounds in ginger, such as gingerol, contributed significantly to the antipyretic effect. Moreover, the cooling agent's effect would primarily provide an immediate sensation of temperature relief, while the gingerol in the formulation likely contributed to a sustained reduction in fever by inhibiting prostaglandin synthesis. Therefore, the combined effects of both the cooling agent and gingerol contributed to the observed results, with gingerol playing a central role in the antipyretic action. Its optimal viscosity, pH stability, and prolonged adhesion time contributed to its superior performance, ensuring efficient absorption of active compounds. The 3% and 10% formulations, while effective to varying degrees, were limited by lower active compound content and high viscosity, respectively. These findings underscore the importance of balancing formulation properties to achieve optimal therapeutic outcomes. This study highlights the potential of red ginger hydrogel as an effective antipyretic treatment and provides valuable insights into the development of herbal-based topical preparations. Future research should explore this formulation's scalability and clinical applications, aiming to integrate traditional remedies like red ginger into modern therapeutic practices for broader healthcare benefits.

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