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Formulation and Antipyretic Evaluation of Papaya Root Extract (*Carica papaya* L.) Hydrogel Patch in Male Mice

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ABSTRACT

Papaya root (*Carica papaya* L.) has traditionally been used to manage fever, but its development as a standardized topical antipyretic preparation remains limited. Therefore, this study aimed to formulate hydrogel patches containing 5%, 10%, and 12.5% ethanolic papaya root extract and evaluate their physicochemical characteristics and antipyretic activity in DPT-HB vaccine-induced febrile male mice. Twenty-five mice (*Mus musculus* L.) were randomly allocated to a negative control, a positive control, and three extract-patch groups (n = 5 each). Rectal temperature was measured before fever induction and at 0, 15, 30, 45, and 60 minutes after treatment. Data were analyzed by one-way ANOVA followed by Tukey's HSD test. All formulations were homogeneous, semi-solid, brownish patches with pH values of 5.7–5.8 and viscosities of 176,000–236,000 cP. At 60 minutes, temperatures were 38.2°C in the negative control, 36.9°C in the positive control, 36.7°C in the 5% group, 36.9°C in the 10% group, and 36.6°C in the 12.5% group. Significant differences were found among groups ($p = 0.033$), and the 12.5% formulation showed the largest observed temperature reduction. Papaya root extract can therefore be incorporated into a hydrogel patch with acceptable physicochemical characteristics and preliminary antipyretic activity.

Keywords**:** Antipyretic; Carica papaya, Hydrogel patch; Mice: Papaya root; Topical delivery

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INTRODUCTION

Fever is a regulated elevation of body temperature that commonly accompanies infectious and inflammatory conditions. Normal body temperature varies among individuals and measurement sites, whereas fever reflects an upward shift in the hypothalamic temperature set point rather than uncontrolled hyperthermia [1]. During inflammation, cytokines including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α stimulate cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) production, thereby increasing the hypothalamic temperature set point [2–4]. Appropriate management is therefore required to relieve discomfort, maintain hydration, and identify underlying conditions that require medical treatment.

Fever management generally combines clinical assessment, pharmacological antipyretics, adequate fluid intake, and supportive physical measures. Cooling gels and patches are used primarily to provide local cooling and comfort, particularly in children [5]. Nevertheless, their effect is generally physical and supportive, and they do not replace systemic antipyretic therapy or medical evaluation. Incorporating bioactive compounds into a wearable patch may extend skin contact and create a more practical delivery system [6].

Medicinal plants remain important sources of compounds with anti-inflammatory and antioxidant activities. The World Health Organization recognizes traditional and complementary medicine as an important component of healthcare while emphasizing the need for evidence concerning efficacy, safety, standardization, and quality control [7]. Flavonoids and other phenolic compounds can modulate inflammatory pathways, including COX activity and PGE2 production [8–11]. Papaya (*Carica papaya* L.) contains alkaloids, flavonoids, saponins, phenolics, and other phytochemicals associated with antioxidant and anti-inflammatory activity, and its root has been used traditionally as a fever remedy [12,13].

Despite this traditional use, pharmaceutical development of papaya root remains limited. Published studies have focused more frequently on papaya extracts in general and on the leaves or seeds than on the root [12–16]. Evidence concerning the incorporation of papaya root extract into a hydrogel patch for fever management is therefore scarce. In addition, traditional decoctions may be affected by variable dosing, limited stability, short storage duration, and reduced practicality, creating a need for a more standardized and convenient dosage form.

Hydrogels are three-dimensional hydrophilic polymer networks capable of retaining water and supporting the diffusion of incorporated compounds [17,18]. In topical and transdermal systems, hydrogel matrices can provide prolonged contact, reduce loss of the formulation, and improve user comfort and dosing consistency [19–21]. The novelty of this study lies in combining papaya root extract with hydrogel patch technology as a topical supportive approach to fever management. Accordingly, this study aimed to formulate hydrogel patches containing different concentrations of papaya root extract, evaluate their physicochemical characteristics, and determine their antipyretic activity in DPT-

HB vaccine-induced febrile male mice (*Mus musculus* L.).

METHODS

The instruments used in this study included a drying cabinet, blender, extraction vessels, animal balance (Ohaus), analytical balance (Mettler Toledo), rotary evaporator (Eyela), VR-3000 viscometer, filter paper, glassware (Pyrex), water bath, dropping pipettes, 1 mL syringes (One Med), feeding tubes, aluminum foil, stopwatch, digital thermometer, funnel, pH meter, hot plate, magnetic stirrer, test tubes, and hydrogel patch molds. The materials consisted of papaya roots, 96% ethanol, sodium carboxymethyl cellulose (Na-CMC), glycerin, nipagin, propylene glycol, distilled water, DPT-HB vaccine, CMC preparation, a commercial antipyretic patch, phytochemical reagents, and other analytical-grade materials. Papaya roots (*Carica papaya* L.) were authenticated by a botanist from the Department of Biology, Universitas Sumatera Utara, and a voucher specimen was deposited at Herbarium MEDA under voucher number 4644/MEDA. Dried papaya root simplicia was extracted by percolation using 96% ethanol, and the resulting percolate was concentrated using a rotary evaporator at a temperature below 50°C to minimize degradation of thermolabile constituents. The concentrated extract was stored in an airtight container at 4–8°C until formulation and analysis. Qualitative phytochemical screening was performed on the papaya root simplicia powder and ethanolic extract to identify alkaloids, flavonoids, saponins, tannins, anthraquinone glycosides, and steroids/terpenoids. Hydrogel patch formulations were prepared using Na-CMC as the polymer matrix and pharmaceutical excipients selected according to established excipient and physical-pharmacy principles [22,23]. Three extract concentrations—5%, 10%, and 12.5%—were evaluated. The composition of each formulation is presented in Table 1.

Table 1. Hydrogel Patch Formulation

Ingredients	F1 (5%)	F2 (10%)	F3 (12.5%)
Papaya Root Extract (*Carica papaya* L. Radix)	5 g	10 g	12.5 g
Na-CMC	1.25 g	1.25 g	1.25 g
Glycerin	2.0 g	2.0 g	2.0 g
Nipagin	0.075 g	0.075 g	0.075 g
Propylene glycol	1.0 g	1.0 g	1.0 g
Distilled water	ad 30 g	ad 30 g	ad 30 g

This randomized controlled laboratory study employed a completely randomized design involving 25 healthy male mice (*Mus musculus* L.) aged 8–12 weeks and weighing 25–40 g. The mice were randomly allocated into five groups (n = 5 per group): a negative control receiving a CMC preparation, a positive control receiving a commercial antipyretic hydrogel patch, Formula 1 containing 5% papaya root extract, Formula 2 containing 10% extract, and Formula 3 containing 12.5% extract. Rectal temperature measurements were conducted under blinded conditions to minimize observer bias. The animals were obtained from the Animal Laboratory Unit of Universitas Muslim Nusantara Al-Washliyah and acclimatized for seven days at 22–25°C and 50–60% relative humidity under a 12-hour

light–dark cycle, with unrestricted access to food and water. Animal handling followed humane endpoint principles [24], and ethical approval was granted by the Animal Ethics Committee of Universitas Sumatera Utara under approval number 000466/KEPH-FMIPA/2024. Nipagin was dissolved in hot distilled water, while Na-CMC was hydrated separately to form a homogeneous gel base. The nipagin solution, glycerin, propylene glycol, and papaya root extract were gradually incorporated under continuous stirring until a uniform hydrogel was obtained. The hydrogel was cast onto micropore surgical tape with a polyurethane backing, formed into 4 × 8 cm patches, and dried at 25°C for 24 hours. The formulations were evaluated for color, odor, texture, appearance, pH, homogeneity, and viscosity. For pH determination, 2.5 g of hydrogel was dispersed in 25 mL of distilled water, equilibrated for two hours, and measured in triplicate using a digital pH meter. Homogeneity was assessed by examining samples from different layers for particles, aggregates, and phase separation. Viscosity was measured in triplicate at 25 ± 2°C using a VR-3000 viscometer equipped with spindle No. 6 at 60 rpm. Before the antipyretic activity test, the mice were fasted for eight hours while retaining free access to water. Fever was induced by administering the DPT-HB vaccine, following a model previously used in experimental antipyretic evaluation [25]. Rectal temperature was recorded before induction, immediately after fever induction (0 minutes), and at 15, 30, 45, and 60 minutes after patch application. The patches were applied to the shaved dorsal area of each mouse, and the animals were monitored throughout the observation period. Data were analyzed using SPSS version 26. Normality and homogeneity were evaluated using the Shapiro–Wilk and Levene tests, respectively. The longitudinal temperature profile was summarized descriptively at each measurement time. For the primary between-group analysis, the change in rectal temperature from fever induction (0 minutes) to 60 minutes was assessed using one-way analysis of variance (ANOVA), followed by Tukey's honestly significant difference post hoc test. Statistical significance was defined as $p < 0.05$.

RESULTS

Phytochemical Screening and Antipyretic Activity

Phytochemical screening showed that both the papaya root simplicia powder and ethanolic extract contained alkaloids, flavonoids, saponins, and steroids/terpenoids, whereas tannins and anthraquinone glycosides were not detected (Table 2). Following DPT-HB-induced fever, the negative control group showed only a slight decrease in rectal temperature from 38.5°C at 0 minutes to 38.2°C at 60 minutes. In comparison, the positive control and the hydrogel patches containing 5%, 10%, and 12.5% papaya root extract reached final temperatures of 36.9°C, 36.7°C, 36.9°C, and 36.6°C, respectively. Formula 3, containing 12.5% extract, showed the fastest observed temperature reduction, reaching 36.6°C at 45 minutes and maintaining this temperature at 60 minutes. One-way ANOVA indicated a statistically significant overall difference among the treatment groups ($p = 0.033$), while Tukey's HSD test showed that Formulas 2 and 3 produced significantly greater temperature reductions than the negative control ($p < 0.05$). Detailed temperature measurements are presented in Table 3.

Table 2. Phytochemical Screening of Papaya Root Simplicia Powder and Ethanolic Extract

Parameter	Simplicia powder	Ethanolic extract
Alkaloids	+	+
Flavonoids	+	+
Saponins	+	+
Steroids/Terpenoids	+	+
Tannins	−	−
Anthraquinone glycosides	−	−

Note: (+) detected; (−) not detected.

Table 3. Mean Rectal Temperature (°C) Before and After Hydrogel Patch Application

Treatment	Normal	Fever (0 min)	15 min	30 min	45 min	60 min
Negative control (CMC)	37.1	38.5	38.4	38.3	38.3	38.2
Positive control	37.2	38.4	38.2	37.8	37.5	36.9
F1 (5%)	36.8	38.3	38.1	37.6	37.3	36.7
F2 (10%)	36.9	38.2	37.9	37.7	37.3	36.9
F3 (12.5%)	36.6	38.3	37.7	37.0	36.6	36.6

Note: Values are presented as means for five mice per group.

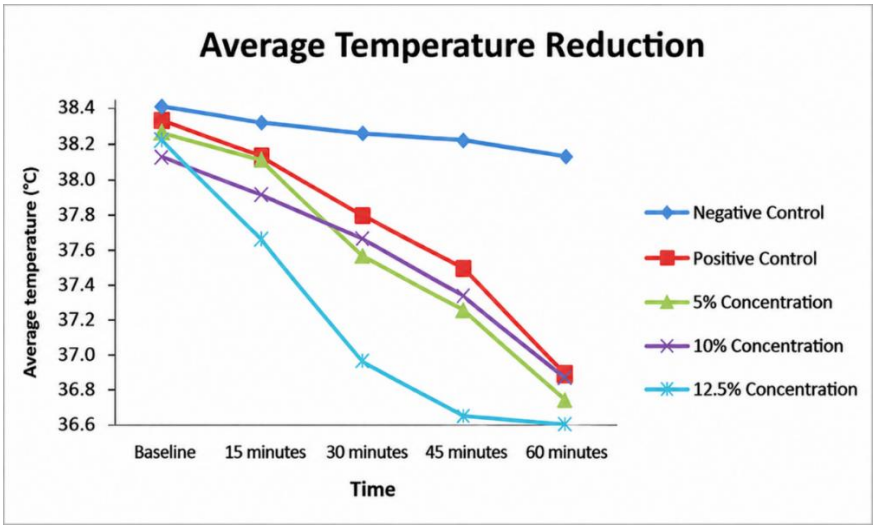

Figure 1. Mean rectal temperature after application of papaya root extract hydrogel patches (*Carica papaya* L. Radix).

Physicochemical Characteristics of the Hydrogel Patches

All formulations produced 4 × 8 cm adhesive hydrogel patches with a semi-solid texture, characteristic extract odor, and homogeneous appearance. Color intensity increased from light brown in Formula 1 to brownish in Formula 2 and dark brownish in Formula 3. The pH values were 5.8, 5.7, and 5.8, while the viscosities were 236,000, 176,000, and 216,000 cP for Formula 1, Formula 2, and Formula 3, respectively (Table 4).

Table 4. Physicochemical Characteristics of Papaya Root Extract Hydrogel Patches

Physical test	**F1 (5%)**	**F2 (10%)**	**F3 (12.5%)**
Odor	Characteristic	Characteristic	Characteristic
Texture	Semi-solid	Semi-solid	Semi-solid
Color	Light brown	Brownish	Dark brownish
pH	5.8	5.7	5.8
Viscosity (cP)	236,000	176,000	216,000
Homogeneity	Homogeneous	Homogeneous	Homogeneous

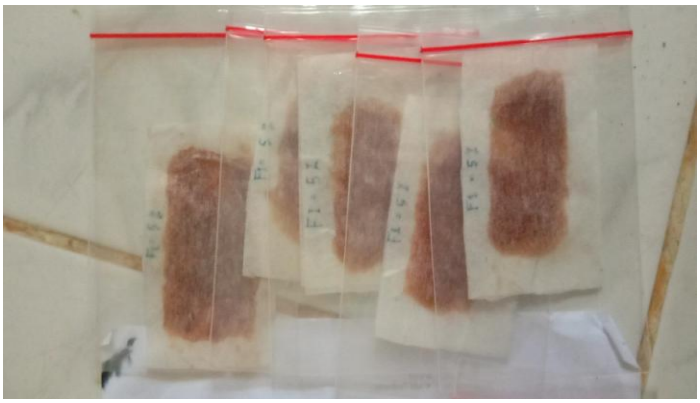

Figure 2. Papaya root extract hydrogel patches prepared on adhesive backing.

DISCUSSION

This study demonstrated that papaya root ethanolic extract could be incorporated into a homogeneous hydrogel matrix and that the resulting patches reduced rectal temperature in DPT-HB vaccine-induced febrile mice. Formula 3 produced the fastest and greatest observed reduction, reaching 36.6°C at 45 minutes, while the negative control remained above 38°C throughout the observation period. The significant overall ANOVA result and post hoc differences for Formula 2 and Formula 3 indicate that the observed response was not attributable solely to the CMC control preparation.

The detection of alkaloids, flavonoids, saponins, and steroids/terpenoids in both the simplicia powder and ethanolic extract is consistent with reviews describing the broad phytochemical composition of *Carica papaya* [12,13]. Studies of papaya leaves and seeds have likewise reported antioxidant and biologically active constituents, although the profile varies according to plant part, extraction solvent, and analytical method [14–16]. The present qualitative screening confirms the presence of several relevant metabolite classes in the root, but it does not establish their concentrations or identify the specific compounds responsible for the biological response.

A plausible explanation for the antipyretic response involves modulation of inflammatory mediators. Fever is driven in part by cytokine-induced COX-2 activation and increased PGE2 synthesis in the central thermoregulatory pathway [2–4]. Flavonoids can reduce PGE2 production and suppress COX-2-related signaling in experimental systems [8–11]. Alkaloids, saponins, and terpenoids may also contribute through anti-inflammatory or antioxidant pathways; however, the present study did not measure cytokines, COX-2, PGE2, oxidative stress, or systemic absorption. The proposed mechanism should therefore be interpreted as biologically plausible rather than directly demonstrated.

The faster observed response of Formula 3 may be associated with the larger amount of papaya root extract incorporated into the hydrogel matrix. However, the antipyretic response was not strictly concentration-dependent because Formulas 1 and 2 produced relatively similar final temperatures. The water-rich hydrogel matrix may also contribute to local cooling [5] while maintaining prolonged contact with the skin and facilitating the diffusion of incorporated compounds [6,17–21]. Nevertheless, drug-release, skin-permeation, and systemic-absorption studies were not performed; therefore, these mechanisms should be regarded as biologically plausible explanations rather than directly demonstrated

effects.

The pH values of 5.7–5.8, homogeneous appearance, and semi-solid texture indicate that stable-looking patches were obtained during the immediate evaluation. Differences in viscosity among formulations suggest that extract concentration influenced matrix structure, which may affect spreading, adhesion, and release behavior in hydrogel systems [17,18,20–23]. Nevertheless, pH and visual homogeneity alone are insufficient to establish dermal safety or long-term product stability. Skin irritation, microbial quality, adhesion, tensile strength, moisture behavior, content uniformity, accelerated stability, and storage studies should be reported comprehensively before further development.

Several limitations should be considered. The sample size was small (n = 5 per group), the observation period was limited to 60 minutes, and the reported temperature table did not include measures of dispersion, effect sizes, or confidence intervals. The study also lacked quantitative phytochemical standardization, pharmacokinetic data, release and permeation testing, and direct assessment of dermal safety. In addition, efficacy in an experimental vaccine-induced fever model cannot be extrapolated directly to clinical fever management in humans. Future studies should use standardized extracts, fully reported dosing and administration procedures, larger samples, repeated-measures analysis where appropriate, longer observation periods, and safety testing consistent with humane experimental principles [24,25].

CONCLUSION

Papaya root ethanolic extract was successfully incorporated into homogeneous hydrogel patches with pH values of 5.7–5.8 and viscosities of 176,000–236,000 cP. The patches reduced rectal temperature in DPT-HB vaccine-induced febrile mice, and the 12.5% formulation produced the greatest observed reduction, reaching 36.6°C at 45 minutes and maintaining this temperature at 60 minutes. These findings provide preliminary evidence that papaya root extract hydrogel patches may have potential as a topical supportive antipyretic preparation. Further research is required to standardize the extract, confirm release and permeation, evaluate stability and dermal safety, and determine efficacy in appropriately designed clinical studies.

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