

Hydrogel Biopatch from Extracts Aloe vera, Centella asiatica, and Erythrina subumbrans for Fever Treatment

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Abstract

Fever is an increase in body temperature above normal due to the body's immune protection. However, high fever can make children uncomfortable and worsen dehydration. Parents often use cooling patches as an easy, effective, and comfortable way to reduce fever in children. Yet, some children may be prone to allergies to commercial patch ingredients. To address this issue, we developed a new hydrogel. We formulated a biopatch made from Aloe vera, Centella asiatica, and Erythrina subumbrans extracts due to their high flavonoid content, antipyretic, and antioxidant effects. The hydrogel's effectiveness was evaluated through organoleptic tests, pH tests, and temperature reduction tests on animal subjects. The subjects were divided into four groups (5 animals/group): positive control, negative control, and combinations of extracts F1, F2, and F3. The temperature reduction test showed that the F2 extract combination provided good results. The pH test showed an average pH of 5-6. The active ingredients of Aloe vera, Centella asiatica, and Erythrina subumbrans were shown to provide antipyretic effects and work synergistically to increase the effectiveness in reducing fever. The combination of the three ingredients was also shown to have a significant fever-reducing effect based on testing compared to the control.

Keywords : biopatch, fever reducer, herbal, hydrogel.

INTRODUCTION

Fever is an increase in body temperature above 37°C due to inflammation and a response to the entry of foreign objects (pathogens) into the body [1]. This is quite dangerous for toddlers because they do not have full awareness of their physical condition which is prone to seizures due to body temperature exceeding 40 °C [2]. If these symptoms are left unchecked, the effects can cause permanent brain damage, so in general, toddlers who experience fever are given heat-reducing syrups that are practical in use. However, in mid-2022, hundreds of cases of kidney failure that attacked children aged 1-5 years emerged, causing casualties with 189 cases in several provinces in Indonesia [3].

Cases of acute renal failure affecting toddlers are identified with symptoms of fever that has not subsided for 3 to 5 days, cough with phlegm, and a decrease in the amount of urine volume marked by

infrequent urination activity. This phenomenon occurs because some fever-reducing syrups are known to have been contaminated with diethylene glycol and ethylene glycol, which have an effect on the formation of crystals in the kidney organs. The crystals are identified as insoluble oxalic acid calcium salts, and are formed in oxalic acid fluid solutions with calcium ion levels in certain chemical conditions that cause clinical disorders such as cytotoxic effects that have an impact on renal tubular obstruction to cause acute kidney failure [4].

The phenomenon of acute renal failure that occurs raises public attention to the use of fever-reducing drugs in the form of syrup preparations to switch to cooling gel patches that effectively relieve body heat due to fever. Cooling gel patches contain a high percentage of water to circulate the body's heat transfer and maintain a constant cool gel temperature. This circulation can relieve high body

temperature due to fever [5]. However, the effectiveness of cooling gel patches has potential side effects in the form of irritation due to the use of synthetic materials contained. To minimize the potential side effects, the synthetic ingredients contained can be replaced by some herbal ingredients. The herbal content, for example, such as leaves from Aloe vera, Centella asiatica, and Erythrina subumbrans which have bioactive ingredients that can be used as cooling gel patches in the form of hydrogels [6].

METHOD

This type of research uses an experimental method that aims to determine the effect of herbal hydrogel patches on antipyretic and antimicrobial.

Extract Preparation

The main samples of this research are Aloe vera, Centella asiatica, and Erythrina subumbrans Dry sorting is carried out then mashed into powder ready for extraction. Simplisia that has been mashed, put into a maceration container and then added 96% ethanol solvent in a ratio of 1: 5 (material: solvent). Maceration was carried out for 3x24 hours with occasional stirring then remaceration of the filtrate obtained for 1x24 hours. The filtrate from maceration was concentrated using a rotary evaporator until a thick extract was obtained. It takes 3 kg of each simplisia to obtain 20 grams of extract [7].

Patch Making

A total of 0.8 g HPMC was dissolved with 100 mL of distilled water, then stirred on a hotplate until homogeneous. Next, it was mixed with 0.8 g ethyl cellulose which was dissolved with 100 mL of distilled water. Menthol was made with a concentration of (1gr/100ml 96% alcohol) and poured as much as 16 mL into the mixture. Finally, the extract was poured according to the formulation and the mixture was stirred on a hotplate until homogeneous with a slightly thick texture.

Table 1 Formulation of Patch Making Materials

Material	Function	F1	F2	F3
HPMC	Gel base	1 gr / 100 ml aq	1 gr / 100 ml aq	1 gr / 100 ml aq
Etil Selulosa (EC)	Increases viscosity	1 gr / 100 ml aq	1 gr / 100 ml aq	1 gr / 100 ml aq
PEG 400	Plastilizer, improve elasticity	32 mL	32 mL	32 mL
Menthol	Increases penetration	32 mL	32 mL	32 mL
Ekstrak Dadap	Active substance	0,54 gr	0,84 gr	0,36 gr
Ekstrak Pegagan	Active substance	0,36 gr	0, 54 gr	0,84 gr
Aloe Vera	Active substance	0,84 gr	0,36 gr	0,54 gr

Temperature Reduction Test

Mice were divided into 5 treatment groups, namely group 1 was given a patch without extract as a negative control, group 2 was given a commercial patch as a positive control, group 3 was given an extract with formulation 1, group 4 was given an extract with formulation 2, group 5 was given an extract with formulation 3. After giving the test sample and being acclimatized to room conditions, an induction of an increase in body temperature was carried out by injecting 5% peptone subcutaneously in each group at a dose of 0.01 mg/g BW [8].

Folding endurance test

The folding resistance test is done manually by folding the patch repeatedly on the same line until it breaks or is folded up to 300 times [9].

pH test

This test was carried out by adding 10 ml of CO₂-free distilled water to the patch and allowed to stand for 1 hour. This test was carried out using universal pH paper [10].

Phytochemical Screening

Phytochemical tests were carried out to qualitatively determine the levels of

flavonoids, tannins, and phenols from a combination of extracts of Aloe vera, Centella asiatica and Erythrina subumbrans.

Antibacterial Test

Antibacterial testing was carried out using the diffusion method. The bacterial suspension that has been adjusted to McFarland's standard is taken 100 µl and spread on the solidified agar media, then from the petridish, the patch matrix of each formula is taken and then printed with a 6 mm disk mold after printing, the patch matrix of formula 1, formula 2, formula 3, patch matrix without extract, antibiotic control, namely Ampicillin, solvent control, namely 2% tween and paper blank containing a single extract on the solidified media. Incubated at 37° C for 24 hours. Visually observed the inhibition zone and then measured the inhibition zone [11].

RESULT

Temperature Reduction Test Results

Testing the antipyretic effect using hydrogels which are divided into 5 treatment groups, including group 1, namely the administration of fever patches in general (positive control); group 2, namely the administration of hydrogel plaster without extracts (negative control); group 3, namely the administration of hydrogels of ethanol extracts of Aloe vera, Centella asiatica and Erythrina subumbrans (0.54 gr ; 0.36 gr; 0.84 gr); group 4 is the administration of hydrogel ethanol extracts of Aloe vera, Centella asiatica and Erythrina subumbrans (0.84 gr; 0.54 gr; 0.36 gr) and group 5 is the administration of hydrogel ethanol extracts of Aloe vera, Centella asiatica and Erythrina subumbrans (0.36 gr; 0.84 gr; 0.54 gr). Each treatment group was repeated 4 times. Before being treated with hydrogel patches, all groups of mice were induced first with a peptone solution of 0.01 ml/g BW subcutaneously [12].

Table 2 Temperature Measurement Test Results

No	Treatment	Initial Temperature	Fever Temperature	Fever Temperature Decrease (°C) at Minute-			
				15	30	45	60
1.	Bye - Bye Fever	36,6	38.3	38.2	37.9	37.6	37.3
2.	F0	36,8	37.7	37.5	37.6	37.4	37.2
3.	F1	36,7	38.2	37.9	38.1	37.8	37.5
4.	F2	36,5	39	38	38	37	37
5.	F3	36,7	37.9	38.2	37.8	37.4	36.9

Phytochemical screening aims to determine the content of the class of compounds contained in ethanol extracts of Aloe vera, Centella asiatica and Erythrina subumbrans. The results of phytochemical screening can be seen in Table 3.2.

Table 3 Phytochemical Screening Results

No	Parameters	Centella asiatica	Erythrina subumbrans	Aloe Vera
1.	Alkaloid (mayer)	+/positive	+/positive	+/positive
2.	Alkaloid (dragendorff)	+/positive	+/positive	+/positive
3.	Flavonoid	+/positive	+/positive	+/positive
4.	Tanin	+/positive	+/positive	+/positive
5.	Phenol	+/positive	+/positive	+/positive
6.	Steroid	+/positive	+/positive	+/positive
7.	Terpenoid	+/positive	+/positive	+/positive

8.	Saponin	+/-positive	+/-positive	+/-positive
9.	IC 50 (antioxidant activity in ppm)	52,447	52,447	58,36

Organoleptic Test Results

Organoleptical examination of the hydrogel patch preparation aims to observe any changes in shape, color, and odor after one week of storage. The results of the organoleptic test can be seen in Tables 3.3, 3.4, and 3.5.

Table 4 Organoleptic Test Results Texture

Texture	Solid	Semi Solid	Liquid
K-	6	15	10
K1	12	17	2
K2	17	12	2
K3	7	9	15

Table 5 Organoleptic Test Results Color

Color	Conspicuous	Inconspicuous
K-	12	19
K1	23	8
K2	29	2
K3	26	5

Table 6 Organoleptic Test Results Odor

Odor	Pungent Odor	No pungent odor
K-	12	19
K1	26	5
K2	7	24
K3	9	22

pH Test Results

The results of the pH test of hydrogel preparations of ethanol extracts of Aloe vera, Centella asiatica and Erythrina subumbrans can be seen in Table 3.6.

Table 7 pH Test Results

No	Formulation	pH
1.	Patch hydrogel Kontrol	± 7
2.	Patch hydrogel Formula I	± 6
3.	Patch hydrogel Formula II	± 6
4.	Patch hydrogel Formula III	± 6

The pH test of the preparation is one of the most important things to consider in making pharmaceutical preparations for the outside of the body, because if the pH does not meet the body's pH criteria (around 4.5 - 7.0) it can cause irritation to the skin [13].

Folding Endurance Test Results

Folding resistance testing is performed on hydrogel patches with the same folding position repeatedly until a tear appears on the patch. The amount of folding is considered as the value of resistance to folding. Increased folding resistance of a hydrogel patch indicates that the patch has good film consistency, so it is not easily broken or torn during storage.

Table 8 Patch Folding Endurance Test Results

No	Formulation	Amount
1.	Patch hydrogel Control	± 500 folds
2.	Patch hydrogel Formula I	± 230 folds
3.	Patch hydrogel Formula II	± 350 folds
4.	Patch hydrogel Formula III	± 32 folds

Antibacterial Test Results

Flavonoid active ingredients in Erythrina subumbrans in patch preparations to inhibit bacterial growth. From this study, it was obtained that all formulas can inhibit bacterial growth but formula IV has the largest inhibition zone of 1.667 cm. The inhibition zone of formula IV is almost the same as the standard inhibition zone of flavonoids which is 2.067 cm, so it can be ascertained that patch formula IV can prevent fever caused by inflammation by inhibiting bacterial growth.

DISCUSSION

Based on the antipyretic effect testing using hydrogel across five treatment groups, it was found that Groups 3, 4, and 5, which were formulations

combining extracts of *Centella asiatica*, *Erythrina subumbrans*, and *Aloe vera*, showed significant speed and acceleration in temperature reduction. When comparing these three formulations to the temperature-reducing effect of Group 1, the positive control (Bye-Bye Fever), no significant difference was observed due to the similar time ranges of temperature reduction in their respective antipyretic activities.

The antipyretic properties of the three formulated groups compared to Group 1, the positive control, differ in their mechanisms of temperature reduction through antipyretic activity. Group 1, as the positive control, exhibits antipyretic activity through hydrotherapy, involving the circulation of heat transfer within the body, providing a soothing effect. On the other hand, the three formulated groups exhibit antipyretic activity by inhibiting cyclooxygenase, which reduces prostanoid materials in brain areas sensitive to pyrogens and inhibits the synthesis of prostaglandin E2 (PGE2) near the hypothalamic area. This mechanism lowers the thermoregulatory threshold (human body temperature) and serves as the primary antipyretic activity, leading to faster temperature reduction than Group 1 [5].

CONCLUSION

Based on the results and discussion, it can be concluded as follows :

1. Based on physical characteristic parameters, herbal hydrogel patch with formulation II has better texture, odor, and folding resistance than other formulations, but formulation I has a more attractive color. Based on chemical characteristics, a neutral pH was obtained for all formulations.
2. Based on the results of testing on mice, the results obtained

effectively reduce the temperature of mice by 2 °C in formulation II. As for formulations I and III, a less significant decrease was obtained.

3. The active ingredients of *Aloe vera*, *Centella asiatica* and *Erythrina subumbrans* can provide antipyretic effects and have a synergistic relationship to increase the effectiveness in reducing fever.
4. The combination of *Aloe vera*, *Centella asiatica* and *Erythrina subumbrans* is proven to have a heat-reducing effect as evidenced by testing and comparison with the control.

THANK YOU NOTE

I Gusti Ngurah Agung Adi Primantara, Nyoman Maha Dananjaya S. K., I Gusti Agung Istri Mas Dianti Pratiwi, Ayu Sagung Mas Wulan Kesvari Dwi Sutanegara, and Ida Bagus Abiananda Prabaswara, Faculty of Medicine and Health Sciences, Universitas Warmadewa (FKIK Unwar), prepared this journal article based on the report Novel Hydrogel Biopatch from Leaf Extracts of *Aloe vera*, *Centella asiatica*, and *Erythrina subumbrans* for Fever Treatment. This work has been funded by FKIK Unwar under the Student Creativity Programme 2023. The opinions expressed herein are those of the authors and do not necessarily reflect the views of funding agency.

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