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Research Article

Formulation of Wound Healing Hydrogel from 70% Ethanol Extract of Kelakai Roots (*Stenochlaena palustris* (Burm. F.) Bedd) with Polymer Combination of PVA/HPMC

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ABSTRACT

Kelakai root contains alkaloids, saponins, tannins, and flavonoids. This compound is known to have medicinal properties such as wound healing. The effectiveness of wound healing increased by using hydrogel to deliver the active substance. The use of polymers played a role in delivering the active substance. This study aimed to formulate hydrogels for wound healing with various concentrations of polyvinyl alcohol (PVA) and hydroxy propyl methyl cellulose (HPMC) K4M. Preparation of hydrogel by the solvent casting method used 0.2% Kelakai root extract. The physical characteristics of hydrogel investigated before and after the stability test included organoleptic, weight uniformity, thickness, pH, moisture content, and hedonic test of Kelakai roots extract hydrogel. The optimum formula was tested for wound healing activity. The data obtained were then analyzed using Wilcoxon tests with $p<0.05$ considered significant. Physically, Kelakai root extract hydrogel met the test requirements. The results of the wound-healing activity showed that the hydrogel extract of the Kelakai root was able to heal the wounds within seven days. There was a significant difference in wound healing time with $p=0.014$. The optimum formula obtained based on the stability test was F4 with a 1:4 ratio of PVA and HPMC.

INTRODUCTION

Kelakai is one of the wild plant species in Indonesia, especially in Kalimantan. The leaves, roots, stems, and shoots of Kelakai can be used as food and medicine. Several studies have identified that the chemical compounds of the roots of Kelakai include alkaloids, saponins, tannins (Fahruni *et al*., 2018), and flavonoid compounds (Kusmardiyani *et al*., 2016), which are useful as anti-inflammatory, antimicrobial, and antioxidant agents (Margono *et al.,* 2010). Ethanol extract of the Kelakai roots has an IC50 value of 19.06 ppm (Adawiyah & Rizki, 2018). Antioxidants can help prevent damage due to cell oxidation, thereby increasing wound healing (Mohanty, 2017). One type of antioxidant compound is flavonoids, which help in wound healing by inhibiting the lipid peroxidation process. Flavonoids also can eliminate free radicals, assist DNA synthesis, and inhibit the inflammatory process. There are two main anti-inflammatory mechanisms: first by inhibiting capillary permeability and arachidonic acid metabolism, and second by affecting lysosomal secretion of enzymes from neutrophils and endothelial cells (Miladiyah & Prabowo, 2012). Flavonoids have an important role in maintaining permeability and increasing capillary vascular resistance because inflammation leads to increased capillary permeability, so that blood (especially blood plasma) will come out of the capillary network, then followed by an inflammatory response. Flavonoids act on the microvascular endothelium to reduce inflammation (Fitriyani *et al*., 2011).

The effectiveness of wound healing increases by using hydrogel preparations to deliver the active substance to the injured skin. Hydrogels have a three-dimensional shape consisting of cross-linked hydrophilic polymers that are capable of holding large amounts of water or biological fluids (Peppas et al., 2000). The high water content of the polymer contributes to its biocompatibility. Because they resemble natural tissue, hydrogels have many medical and pharmaceutical applications, including the manufacture of contact lenses, membranes for biosensors, materials for artificial skin, and drug delivery devices. Hydrogel is one of the preparations used to heal wounds because it can maintain skin moisture and has optimum hydration ability. Another property of a hydrogel is that it is not sticky so it can reduce pain. The most important component of the material in hydrogel preparations is namely polymer, which acts as a matrix to deliver active substances that penetrate the skin. The polymers used in this study are polyvinyl alcohol (PVA) polymers and hydroxy propyl methyl cellulose (HPMC) K4M. The advantages of PVA polymers are that they have hydrophilic properties, so they are water-selective, resistant to oils, fats, and solvents, odorless, non-toxic, and flexible (Shalumon *et a*l., 2010). Additionally, the advantages of the HPMC K4M polymer are that it has hydrophilic properties, can produce strong hydrogels, is not brittle, and has flexibility (Jayaprakash *et al*., 2010).

Hydrogel is one of the preparations used in wound healing because it can maintain skin moisture and has optimum hydration ability. The polymer is components of a hydrogel formulation. The polymer acts as a matrix to deliver active substances that penetrate the skin. The polymers used in this study are polyvinyl alcohol (PVA) and hydroxy propyl methyl cellulose K4M (HPMC K4M). PVA is a hydrophilic polymer, non-toxic, biodegradable and biocompatible. Chemically, PVA is a semicrystalline copolymer of vinyl acetate and vinyl alcohol. PVA is able to form a good film for the preparation of hydrogels. Structural modification is done by combining other components into the matrix to form good film characteristics. The combined use of PVA with nanocrystalline cellulose in the manufacture of hydrogels has a good impact on the hydrogel properties due to the increase in hydrogen bonding between the hydroxyl groups in the cellulose molecular chain and PVA (Baghaie *et al*., 2017; Kamoun, 2015). HPMC as a film-forming substrate, is a cellulose ether derivative with good biocompatibility, swelling, and thickening properties. We introduced HPMC into PVA to prepare an indicator hydrogel with excellent physical functions. The advantages of PVA polymers are that they have hydrophilic properties, resistant to oils, fats, and solvents, odorless, non-toxic, and flexible. Meanwhile, the advantages of the HPMC has hydrophilic properties, can produce ideal hydrogels, is not brittle, and has flexibility (Jayaprakash *et al*., 2010; Huang *et al*., 2020). Based on this background, this study aimed to formulate hydrogels for wound healing with various concentrations of PVA and HPMC K4M and test the wound healing activity of hydrogel 70% ethanol extract of the root of Kelakai (*Stenochlaena palustris* (Burm. F.) Bedd.) with a combination of PVA and HPMC K4M polymers.

METHODS

Materials

Simplicia of Kelakai roots, glycerin (Bratachem, Indonesia), methyl paraben (Bratachem, Indonesia), PVA (Bratachem, Indonesia), and Propylene glycol (Bratachem, Indonesia), and 70% ethanol (Merck, Germany).

Processing of Kelakai Simplicia

Simplicia processing was done by separating the leaves, stems, and roots of Kelakai. Wet sorting aims to separate the roots from other parts and impurities, then the roots of the Kelakai are washed. The roots of the Kelakai were then cut into small pieces, then dried by aerating for 1-3 days. Next, it was crushed using a blender until it becomes a simplicia powder of the Kelakai roots (Forestryana, 2020).

Preparation of Kelakai Root Extract

The extraction of the root of the Kelakai was conducted by the maceration method. 100 g of sample were extracted using 70% ethanol solvent in a ratio of 1:10 for 3x24 hours with solvent changes every 24 hours. The liquid extract was then separated from the residue using filter paper. Remaceration was performed two times. The liquid extract obtained was concentrated using a rotary evaporator at a temperature of not more than 50°C and evaporated over a water bath until a thick extract was formed (Jamshidi *et al*., 2014).

Phytochemical Screening

Phytochemical screening of the ethanolic extract of the Kelakai root includes testing for flavonoids, tannins, saponins, phenols, alkaloids, and steroids/triterpenoids.

Antioxidant Test of 70% Ethanol Extract of Kelakai Root Qualitatively

The 70% ethanol extract of Kelakai roots was weighed as much as 50 mg then dissolved into 10 mL of ethanol. The thin layer chromatography (TLC) plate was activated before use by placing it in an oven at a temperature of 105°C for 30 minutes which was used as the stationary phase. The solvent used for the eluent was by the optimization results. The 70% ethanol extract of the root of the Kelakai was spotted on the TLC plate using a capillary tube. The elution process was done by inserting the TLC plate into the chamber containing chloroform: methanol (1:2). The eluent was allowed to elude up to the plate. Then, TLC plate was sprayed with 0.1 mm of 2,2-diphenyl-1-picrylhydrazyl (DPPH) solution (Rijai *et al*., 2019). The spots on the TLC plate that have antioxidant activity will turn yellow with a purple background (Kuntorini & Astuti, 2010).

Preparation of Kelakai Roots Ethanol Extract Hydrogel

The hydrogel formula for 70% ethanol extract of the roots of Kelakai can be seen in Table 1. Preparation of hydrogel was done by solvent casting method. First, all of the ingredients used were weighed. PVA was dissolved in hot water in a beaker glass until it dissolves, then the extract of Kelakai roots was dissolved using propylene glycol. HPMC K4M was dispersed using distilled water until completely dispersed. Next, each of these solutions were mixed and stirred until homogeneous. Then, methylparaben, PEG 400, and glycerin were added into the mixture, and 100 mL of distilled water were also added. Then, the solution mixture was poured into a 10 mL petri dish (diameter 60 mm x 15 mm), and allowed to cool at room temperature (22-25°C) until a hydrogel with a diameter of 60 mm and a thickness of 0.5-1.0 mm formed. The hydrogel obtained was then wrapped in aluminum foil and put in a desiccator until it was ready to be evaluated (Roy *et al*., 2008).

Evaluation of Kelakai Root Ethanol Extract Hydrogel

Organoleptic Test

An organoleptic test was conducted by visual observations which included surface texture, shape, color, and odor of the hydrogel (Forestryana *et al*, 2020).

Weight Uniformity

The weight uniformity test was done by weighing the hydrogels one by one using an analytical balance (Pudyastuti *et al*., 2014).

Folding Endurance

This test was done to identify the elasticity and fragility of the hydrogel matrix. The folding endurance test was conducted manually by folding the hydrogel repeatedly in the same position until it breaks or up to 300 times (Patel *et al*., 2015). The number of folding was considered as the value of folding endurance (Sharma *et al*., 2013).The test results should meet the requirements of the folding endurance formulas more than 300 times (Nurrahmanto *et al*., 2017).

Thickness

Measurement of hydrogel thickness was done using a digital thickness caliper in mm. Thickness measurements were conducted at 5 points of the hydrogel preparation.

Loss in Drying

The hydrogel was weighed and stored in a desiccator for 24 hours containing silica. After 24 hours, the hydrogel was re-weighed, and the percentage of loss from drying was determined (Parivesh *et al*., 2010).

Table 1. Formula of hydrogel Kelakai roots extract

Component	Concentration (%w/v)						
	F1	F2	F3	F4	F5	F6	F7
Extract of Kelakai roots	0.2	0.2	0.2	0.2	0.2	0.2	0.2
PVA	1	2	1	1	4	1	6
HPMC K4M	2	1	1	4	1	6	1
PEG 400	30	30	30	30	30	30	30
Glycerin	2	2	2	2	2	2	2
Methyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Aquades ad	100	100	100	100	100	100	100

PVA, polyvinyl alcohol; HPMC, hydroxypropyl methylcellulose; PEG, polyethylene glycol.

Moisture Content

The hydrogel was placed in a desiccator at 25°C for 24 hours then the films were weighed again one by one after storage in the desiccator. The moisture content of the formula was then calculated. The results of these calculations were expressed as percentage of moisture content (Parivesh *et al*., 2010).
Percentage of moisture content:

%MC =
(Initial weight-Final weight)/(Initial weight) x100%

pH

The surface pH test was conducted using a pH meter with a tolerable pH range of 4.5-6.5 that does not irritate the skin (Walters & Robert, 2015).

Hedonic test

The hedonic test was conducted using a panelist group of 20 people aged 20-35 years (Sumiyati & Mandike, 2017). This test describes the degree of consumer acceptance and satisfaction regarding formula attributes. Panelists were asked to assess how much they liked the texture, color, taste, and aroma of hydrogel. The scale given was as follows: (6) very much like, (5) like, (4) somewhat like, (3) neutral, (2) mostly do not like it, and (1) do not like. The data obtained from the hedonic test results were analyzed by counting the number of frequencies of responses that choose a certain favorite scale.

Determination of Optimum Formula

Determination of the optimum formula was done by looking at the response value of the best moisture content and loss on drying because these two responses affect the stability of the preparation.

Stability Test

The accelerated stability test was conducted using the freeze-thaw method for six cycles at temperatures 4°±2°C and 25°±2°C (Qindeel *et al*., 2019).

In Vivo Wound Healing Activity

This test was done on three rabbits. The hair on the skin of the back of rabbits was removed using a razor blade (10-20 cm). Then, on the surface of the rabbits' back, the area was marked and divided into four parts for treatment. The rabbits' back were anesthetized with ketamine. The incision wound was given using a sterile scalpel with a wound length of 3 cm and a depth of about 2 mm from the skin surface. Before the treatment was given, adaptation was conducted on experimental animals for 7 days kept in animal cages. In each incision wound, the optimum formula was given for the hydrogel of Kelakai roots ethanol extract, extract, blank hydrogel, and povidone iodine. Each treatment was given the treatment on a wound site twice a day for 14 days. The rabbits were given the same diet to avoid the internal variability of each rabbit. Observations were done over 14 days by observing the healing time (Ahmed *et al*., 2019).

Data Analysis

Data analysis used ANOVA statistics with a 95% confidence level to determine any significant differences in each formula. Stability test data were analyzed using an independent sample t-test. The results of wound healing activity were analyzed using ANOVA then continuing with LSD tests. Significant results were determined by $p<0.05$.

RESULTS AND DISCUSSION

The determination of the Kelakai plant (*Stenochlaena palustris* (Burm. F.) Bedd.) was done in the laboratory of the Faculty of Mathematics and Natural Sciences, Lambung Mangkurat University, Banjarbaru. This determination aims to authenticate and ensure that the plants studied are of the correct type. The results of the determination classification stated that the fitness used as the sample was species *Stenochlaena palustris* (Burm. F.) Bedd.). The extract yielded 2.59% of the total 300 g of simplicia. The screening phytochemical showed that the ethanolic extract of Kelakai roots contains flavonoids, phenols, triterpenoids, saponins, alkaloids, and tannins, which follow the results of tests conducted by Fahruni *et al.* (2018). Meanwhile, the qualitative measurements of the antioxidant activity of ethanolic extract of Kelakai roots show that the extract of Kelakai roots has activity antioxidants which are shown by DPPH testing, where the spot on TLC changes in color from purple to yellow (Figure 1) (Kuntorini & Astuti, 2010).

Based on these results, the development of hydrogel preparations with Kelakai roots can be used as a wound healing agent. In this study, the hydrogel uses the polymer PVA/HPMC to combine the mechanical and swelling properties of PVA with the flexibility and high water uptake of cellulose derivatives (Kida *et al*., 2020).

Evaluation of Hydrogel

Based on the results of the organoleptic test, the hydrogel of the ethanolic extract of Kelakai roots produced transparent reddish-brown (Figure 2) and homogenous hydrogel with a smooth texture. The hydrogel has a distinctive aroma of the ethanolic extract Kelakai. In the weight uniformity test (Table 2), the weight ranges from 3.33 to 3.53 g. Weight measurement were done to determine the uniformity of weight hydrogel. PVA is a hydrophilic polymer that affects humidity so that its use in large quantities can affect the weight of the hydrogel. Based on ANOVA, the *p*-value of the weight uniformity was > 0.05, which means there was no significant difference in weight for each hydrogel formula. Thickness measurements were done to identify uniformity of the hydrogel thickness produced. The heavier the hydrogel was, the thicker the resulting hydrogel will be. The number of polymers used as a hydrogel base affects the thickness of the hydrogel. The use of PVA and HPMC as polymers will also increase the thickness of the hydrogel because PVA has hygroscopic properties. The higher the concentration of PVA was, the higher the thickness of the hydrogel will be. The addition of PVA causes the formation of many hydrogen bonds so that water can diffuse on the composite membrane, and PVP can absorb water equal to its weight (Piluharto, 2017). The measurement results (Table 3) show that the thickness of the hydrogel varies from 0.52 to 0.62 cm. The *p*-value obtained for the uniformity of the thickness was $p > 0.05$ which indicates that each formula does not have a significant difference in thickness.

Measurement of moisture content aims to determine the ability of the hydrogel to absorb water from the environment, which can affect the stability of the hydrogel. However, the presence of water in the hydrogel will provide a cooling feeling when applied to the skin. If the water content is too high, it can cause the stability of the hydrogel to be reduced (Shivaraj, 2010). A hydrogel is said to be good if the hydrogel is dry and has little water content so that the hydrogel stability will be good. The required water content range is 1 – 10%. Additionally, the ability to absorb water plays an important role in drug penetration through the skin due to the hydration process. However, the amount of water absorbed can reduce the stability of the hydrogel because the hydrogel becomes sticky and wet and can even become a medium for the growth of microorganisms (Shivaraj, 2010). Based on the results, the hydrogel of the ethanolic extract of Kelakai roots has a relatively low moisture content.

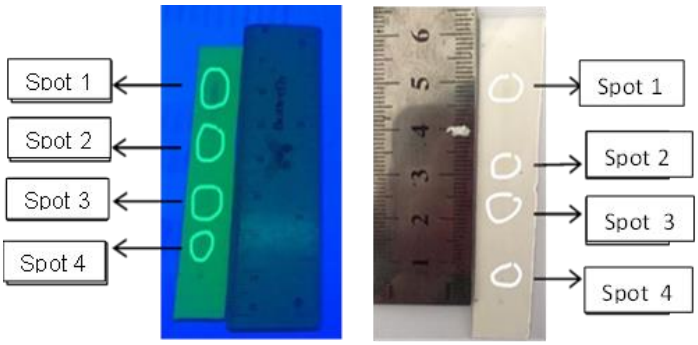

Figure 1. Qualitative antioxidants activity of Kelakai roots extract.

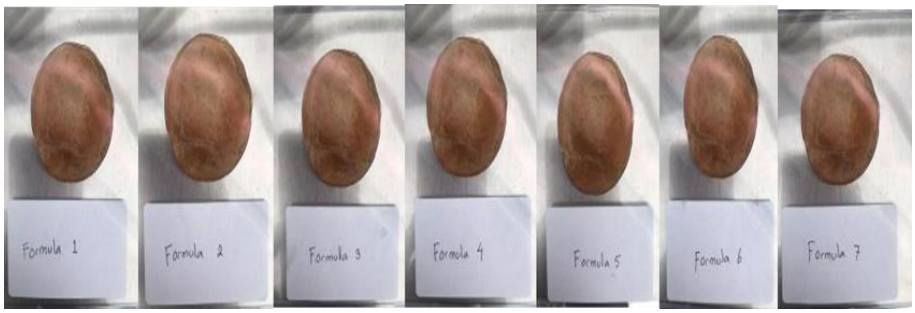

Figure 2. Visual appearance of hydrogel Kelakai roots extract

Table 2. Physical characterization of hydrogels

Formula	Physical Characterization					
	Weight (mg)	Thickness (mm)	Folding endurance	Dry loss (%)	Moisture content (%)	pH
F1	3.53±0.06	0.52±0.01	>300	2.83±0.15	2.44±0.02	6.3
F2	3.37±0.15	0.57±0.03	>300	2.97±0.12	2.92±0.60	6.2
F3	3.50±0.10	0.57±0.03	>300	2.93±0.06	3.43±0.12	6.0
F4	3.33±0.12	0.62±0.06	>300	2.77±0.15	2.15±0.03	6.4
F5	3.43±0.15	0.60±0.03	>300	2.83±0.50	3.04±0.12	6.3
F6	3.37±0.15	0.57±0.05	>300	3.13±0.21	2.70±0.2	6.2
F7	3.33±0.21	0.56±0.02	>300	2.97±0.12	2.72±0.17	6.4

Table 3. Healing time of wound healing activity

Rabbit	Period of epithelization (Days)			
	Hydrogel	Kelakai extract	Blank hydrogel	Povidone solution
M1	8	6	14	7
M2	8	7	14	8
M3	7	6	14	7
Mean ±SD	7.7±0.57	6.3±0.57	14±0	7.3±0.57

SD, standard deviation.

The hydrogels with higher proportions of HPMC presented lower moisture contents, which was because of the formation of hydrogen bonds between the HPMC and PVA. This reduced the amounts of reactive hydrophilic hydroxyl groups on the PVA molecular chain, indicating the addition of HPMC could limit the water absorption ability of PVA. Based on the results of statistical data on hydrogel preparations using one-way ANOVA in each formula, each formula has a p= 0.003 (<0.05), which indicated there was a significant difference in moisture content in variations in the concentration of PVA and HPMC used.

The folding resistance test aims to determine the folding capacity of the hydrogel polymer (Sharma *et al*., 2013). The plasticizer is one of the additives that can affect the physical properties of hydrogel preparations. The plasticizer gives the hydrogel flexibility due to the rigidity of the hydrogel and increases the flexibility of the hydrogel. The results of the folding resistance of all hydrogel formulas have met the requirements because the hydrogel did not break after folding up to 300 times (Jhawat, 2013).

The surface pH test aims to determine the physical stability of the hydrogel preparation, the effectiveness of the preservative, and the condition of the skin. The pH of the hydrogel preparation was at a pH of 6.0-6.4 and this meets the requirements which state that a safe pH that does not irritate the skin for topical preparations is 4.5-6.5 (Sayuti, 2016). For the safe application (without irritation problem) on the skin, the pH of topical formulations should be within the range of skin pH of 4.5–7 (Forestryana, 2020). The pH for all the hydrogel was between 6.28 and 6.54. Therefore, it is assumed that the prepared hydrogel formulations will not produce any harmful effects on the skin (Parhi, 2015)

Determination of the Optimum Formula

Determination of the optimum formula was done by taking test data that meet the requirements. The test selected in determining the optimum formula is the value of percent of moisture content and loss on drying. Percent of moisture content is chosen because the response indicates the amount of water content in the hydrogel preparation, which can affect the stability of the hydrogel. The percent of moisture content requirement is 1-10%. Hydrogel will have good stability if it contains a small amount of water so that it will not be easily contaminated by microorganisms. The percent of moisture content of the seven formulas met the requirements because they were in the range of 2.44% to 3.53%. The moisture content which had the smallest percent of moisture content was formula F4 with 2.44% ± 0.06.

Stability Testing

Based on stability testing using Freeze Thaw cycling, it was found that all of the hydrogel formulas for the extract Kelakai roots were

stable. Based on statistical analysis using independent T - tests, no significant differences were found both before and after the test.

In Vivo Wound Healing Activity

This test was used for the formula 4 as the optimum formula. The activity test aims to determine the effectiveness of hydrogel preparations as wound healing. Testing is done by looking at the time it takes for the wound to heal. Rabbits that have been injured were then given a different treatment once a day (d) on the back of the rabbit which has been divided into 4 parts: one given the extract of Kelakai roots, the hydrogel of the extract of the root of the Kelakai, the hydrogel base as a negative control and one part as a positive control was given povidone iodine. Observations were made for 14 days to see the healing time for each treatment. The wound was said to be healed when the wound I was given has closed. In the *in vivo* wound healing activity test, differences in wound healing time were obtained for each treatment. The average wound healing time for hydrogel Kelakai roots extract was 7.7 d, the extract of Kelakai roots was 6.3 d, negative control (PVA polymer and HPMC K4M) was 14 d, and the positive control (povidone iodine) was 7.3 d (Table 3). From these data, it can be seen that the extract of the root of the Kelakai has a better effectiveness as a wound healing than the hydrogel of the extract Kelakai roots. This is because there is an effect of additives used in the formulation of hydrogel preparations, thus causing the effectiveness of the root of Kelakai to be reduced, but not reducing its effectiveness as a wound healing. While the extract does not use an intermediary in the dosage form, still the method is less effective in administering drugs in wound healing.

Hydrogel dosage form is in the form of a matrix formed due to the use of polymers. The matrix will release the drug slowly because of its function as a release controller. HPMC is used to control drug release. The difference between the hydrogel and povidone results is that povidone iodine is a liquid dosage form, so it will be easier to penetrate than hydrogel preparations. The results of the LSD statistical test can be seen in the Table 4, which shows that the administration of the hydrogel of the extract of Kelakai roots did not have a significant difference from the positive control of povidone iodine, so it can be said that the hydrogel preparation has a good effectiveness as a wound healing.

Table 4. *P*-values of treatment groups by LSD testing

Treatment groups correlation		***P*-value**
Hydrogel of Kelakai extract	Ethanol extract of Kelakai*	0.040
	Blank hydrogel*	0.000
	Povidone_Iodine	0.438
Ethanol extract of Kelakai	Hydrogel of Kelakai extract*	0.040
	Blank hydrogel*	0.000
	Povidone iodine	0.141
Blank Hydrogel	Hydrogel of Kelakai extract*	0.000
	Ethanol extract of Kelakai*	0.000
	Povidone iodine*	0.000
Povidone_iodine	Hydrogel of Kelakai extract	0.438
	Ethanol extract of Kelakai	0.141
	Blank hydrogel*	0.000

*Significant differences (p<0.05).

CONCLUSIONS

In the present work, a polyvinyl alcohol-hydroxypropyl methylcellulose (PVA/HPMC) hydrogel was successfully developed. The delivered content of Kelakai extract and the physicochemical properties of the PVA/HPMC film containing Kelakai extract showed that these formulations were acceptable and suitable for wound healing seven days after incision wound in an Albino rabbits model. In the present study, the rabbits treated with ethanol hydrogel of Kelakai roots showed wound healing activity. These results indicate that PVA-HPMC film with incorporated Kelakai extract significantly enhances the tissue healing process and can be used in skin wound treatment.

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CONFLICT OF INTEREST

There is no conflict of interest between authors.

ETHICAL APPROVAL

All the authors declare that the study protocols were conducted with approval from The Ethical Committee of Medical Research Medical Faculty, University of Lambung Mangkurat. (No.233/KEPK-FK-UNLAM/EC/VII/2020).

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