Original Article

Permeation studies of flavonoid total on Moringa leaves ethanolic extract patch

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ABSTRACT

A Moringa leaves ethanolic extract at a dose of 5%-15% are recommended as an anti-inflammatory agent for topical preparations. A transdermal patch has several advantages, such as ease of application, painlessness, and long-lasting action. Polymer is the most important component in patch performance, and it can be determined using a release and permeation study. This study used a combination polymer of Polyvinyl Alcohol (PVA) and Alpha-cellulose to produce a faster drug release profile. Therefore, this study aimed to determine the permeation profile of flavonoid total from the patch. A flavonoid total model from Moringa leaves ethanolic extract was used, and patches were formulated from a combination of PVA and Alpha-cellulose with a ratio of 1: 2. Subsequently, the patch was evaluated for flavonoid total permeation study using a modified vertical type of Franz diffusion cell equipped with chicken's egg cell membrane. The flavonoid total released from the patch was 26.16% for 5 hours with a diffusion mechanism. Furthermore, the weight of the total flavonoid that was transported through the chicken's egg cell membrane was 104.23 µg for 5 hours. The penetration flux value was $3.27x10^{-6}$ mg.sec^{-1}.cm^{-2} and the membrane permeability value was $2.46x10^{-6}$ cm/sec. The results showed that the Moringa patch can be developed as a topical anti-inflammatory preparation.

Keywords: Moringa leaves, Flavonoid total, Permeation study, Patch, Polymer

Introduction

Indonesia is a country with abundant biodiversity, particularly herbal plants. Based on empirical data, this makes herbal plants a hereditary therapy. According to the statistical data of RISKESDA from 2010-2018, the number of people using traditional herbal medicine has increased to 44.3%. This shows increased public interest in using traditional drugs and traditional health efforts. One of the plants used in conventional medicine is *Moringa oliefera* L. It is called kelor by the Indonesian people. The flavonoid compounds in Moringa leaves have anti-inflammatory mechanisms, inhibiting the cyclooxygenase enzyme's activity [1, 2]. Quercetin is one of the flavonoid groups and a main bioactive component of kelor leaves which has anti-inflammatory activity [3]. Inflammation can occur locally and systemically and can be acute or chronic, causing pathological abnormalities. The skin is one of the common sites of inflammation, hence, the topical anti-inflammatory preparation for local action is widely developed [4]. Topical anti-inflammatory preparations circulating in market, such as gels and creams, still have a disadvantage because of quick absorption. Therefore, they must be repeatedly applied in a day. The patch preparation was selected because it is continuous with one dose for a long time. Moringa leaves ethanolic extract at a dose of 5%-15% are recommended as an anti-inflammatory agent for effective topical preparations. The concentration of flavonols and flavones from the dry base (each 100 g of dry sample) was 5.53 mg luteolin, 409.06 mg quercetin, and 84.48 mg. The most significant amount of flavonol compound in kelor leaves is quercetin [1, 5].

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Polymers are essential components in matrix patch preparation. The patch can be formulated using a combination of hydrophilic and hydrophobic polymers [6]. Furthermore, combining a hydrophilic polymer such as polyvinyl alcohol and alpha-cellulose (1:2) gives promising results for preparing kelor leaves ethanolic extract patch. This is because it produces a patch that meets the requirements for the physicochemical properties of the patch preparation. Using the combination of hydrophilic polymers can increase matrix permeability to ensure a faster drug diffusion through the matrix than the hydrophobic polymers [7]. However, it is necessary to test the quality of the patch, namely stability at temperature change and permeation test. The transport test of the active substances through the membrane is performed using Franz's diffusion cell method. The ability of the active substance to pass across the membrane is measured by the in-vitro test as the cumulative weight of the active substance transported per unit of time. Franz diffusion cells consist of two components: the donor and receptor compartment, which are separated by a membrane [8]. This study used the chicken eggshell membrane because it is similar to the human stratum corneum and is composed of keratin. Also, the patch resistance test was conducted on variations in storage temperature and a transport test through the eggshell membrane. This was to observe the weight of the active substance calculated as quercetin transported from the matrix patch of kelor leaves ethanolic extract using the Franz diffusion cell method.

Materials and Methods

Materials

Moringa leaves powder (CV. Herbadream, Karanganyar, Central Java, Indonesia); Ethanol 96% technical grade (repackaged by PT. Bratachem, Indonesia); quercetin standard (Sigma-Aldrich, Saint Louis, Missouri); PVA (Sigma-Aldrich, Saint Louis, Missouri); alpha-cellulose (Sigma-Aldrich, Saint Louis, Missouri); phenoxyethanol (repackaged by Cipta Kimia); polyethylene glycol 400 (DOW, United States of America); propylene glycol (DOW, United States of America); ethanol 70% technical grade (repackaged by PT. Agung Jaya); aqua dest (repackaged by PT. Agung Jaya); phosphate buffered saline solution of pH 7.4 (repackaged by CV Nitra Kimia). **Instruments:** pH meter (Ohaus Starter300; Newark, New Jersey); analytical digital scale (Sartorius, BP 110, d = 0,001 g; Göttingen, Jerman); analytical digital scale (KERN ABJ, d =0,1 mg; Balingen, Jerman); oven (Memmert; Schwabach, Jerman); stirrer (IKA C-MAG HS 7; Breisgau, Jerman); spectrophotometer UV-Vis (Thermo Scientific Genesys 10S UV Vis; Waltham, MA); micropipette (DLab, United States); Franz's diffusion Cell (modification instruments by Labtech, Yogyakarta, Indonesia); moisture analyzer; petri dish d=5 cm (normax, Portugal); vernier clippers (TOKI, Jepang); hotplate (Maspion, Indonesia); water bath; rotary evaporator (Buchi Labortechnik).

Moringa leaves extraction

The plant determination was performed at the Biology Laboratory, Faculty of Mathematics and Natural Sciences, Universitas Sebelas Maret, Surakarta, Indonesia. Moringa leaves powder of 500 g was macerated for three days in 2.5 liters of ethanol 96% solution (1:5). Subsequently, the macerate was filtered and concentrated with a rotary evaporator at 40°C until the consistency was thick [9]. The percentage yield of the extract was calculated by comparing the weight of the resulting extract to the simplicia. Meanwhile, an organoleptic evaluation was performed by visual observation of the consistency, color, and odor [10]. The extract's moisture content was measured by weighing 1.0 g of the extract in an aluminum pan on a moisture analyzer. This instrument provides heat at 105°C until its moisture content is constant [11].

Quantitative test of the flavonoid total

The quercetin standard of 10 mg was added to 0.3 mL of sodium nitrite 5% ($NaNO_3$). After five minutes, 0.6 mL of 10% aluminum chloride ($AlCl_3$) was added. Subsequently, 2.0 mL of 1.0 M sodium hydroxide (NaOH) was added after another five minutes, and the solution was placed in a measuring flask with distilled water to 10 mL. The absorbance of the solution was measured using a UV-VIS spectrophotometer at a wavelength of 510 nm [12]. The extract of 50 mg was placed in a volumetric tube of 10 mL, and 0.3 mL of sodium nitrite 5% ($NaNO_3$) was added. After five minutes, 0,6 mL of 10% aluminum chloride ($AlCl_3$) was poured into the tube. Subsequently, 2.0 mL of 1.0 M sodium hydroxide (NaOH) was added after five minutes, and the solution was placed in a measuring flask with distilled water to 10 mL. The absorbance of the solution was measured using a UV-VIS spectrophotometer at a wavelength of 510 nm [12].

Moringa leaves patch formulation

The patch matrix formula **(Table 1)** is modified from the optimum formula optimized in previous studies [13]. First, the alpha-cellulose was dissolved in warm water at 50 °C. Furthermore, the PVA solution was stirred using a magnetic stirrer until homogeneous, then PEG 400, propylene glycol, phenoxyethanol, and ethanol 70% were added. Kelor leaves ethanolic extract was added last to the mixture, then stirred using a magnetic stirrer until homogeneous. The mixture is placed in a patch mold. Patches were dried in an oven at 40 °C for 8 hours and then dried at room temperature for 72 hours. Subsequently, they were stored in airtight packaging [14].

Physicochemical stability test of Moringa patch

Organoleptic test was performed by visually observing changes in the patch's shape, color, taste, and odor during storage at room temperature. The pH test was conducted by dissolving the patch matrix into 10.0 mL of distilled water at room temperature and allowed to stand for 20 minutes. Subsequently, the surface pH of the patch was measured using a pH meter [15]. The folding endurance test was performed by folding the patch repeatedly in

the same position until the patch is torn, and the number of folds is considered as the value of endurance to folding [14]. Moisture content test was conducted using a moisture analyzer, and this tool provided heat at a temperature of 105 °C. The moisture content measurement shows the value of the constant moisture content in the patch preparation. The thickness test was performed using a caliper, and the measurement results were averaged. Patch resistance test to temperature changes at variation time was also conducted to determine the effect of temperature on the physicochemical properties of the patch. Patches were tested by being stored at low temperature (4 °C ± 2 °C) for 8 hours and then stored at room temperature (28 °C ± 2 °C) for 16 hours. The test was continued in an oven at high temperature (40 °C ± 2 °C) for 8 hours, after which it was removed and stored at room temperature (28 °C ± 2 °C) for 16 hours. The test is counted as one cycle, and this will be tested for six cycles.

Permeation test

A total of 10 mg of the standard quercetin was weighed and dissolved with ethanol 96% pro analysis in a 10 mL volumetric flask (stock solution I). The solution of stock I of 100 µL was taken into a 10 mL volumetric flask and added with phosphate buffer saline pH 7.4 solution (stock II). Subsequently, the stock II solution was measured for the maximum wavelength in PBS pH 7.4 solution in the wavelength range of 200-450 nm using a UV-Vis spectrophotometer. Stock II solution was taken in the amount of 0.1; 1.5; 3.0; 4.5; and 6.0 mL into a 10 mL volumetric flask, and PBS solution was added to obtain a series of concentrations. Also, the concentration series solution was measured for absorbance with a UV-Vis spectrophotometer at the maximum wavelength of quercetin in PBS pH 7.4 solution. Measurements were performed three times [16], and the calibration curve measurement data were analyzed by linear regression. Therefore, the correlation coefficient (r) value can be seen, indicating its linearity. The acceptable linearity value is 0.99 [17].

The first step was to prepare the membrane for the chicken eggshells by separating them from the shells and soaking the membrane with PBS pH 7.4 solution for 12 hours before use. The receptor compartment on the vertical type of Franz diffusion cell device was filled with 25 mL of PBS pH 7.4 solution. Furthermore, the solution was stirred using a magnetic stirrer with a rotation speed of 50-100 rpm, and the temperature was set to 37±1°C. Furthermore, the procedure was tested for 5 hours by taking of 5 mL sample solution from the receptor compartment and replaced with a PBS pH 7.4 solution of the same volume. Sampling of the solution was conducted t at 0, 2, 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270 and 300 minutes. The sample solution absorbance was measured with a UV-Vis spectrophotometer for the maximum wavelength. Total flavonoids were calculated as quercetin in PBS pH 7.4 solution and PBS pH 7.4 solution as a blank. Based on the absorbance data obtained, the cumulative number of flavonoids transported across the membrane of the chicken eggshell was calculated [16].

For this calculation, Q is the cumulative amount of quercetin per area of diffusion (µg/cm^2); C is the active substant concentration at n minutes (µg/mL); $\sum^{n-1}$ Ci is the amount of quercetin concentration (µg/mL) in the first sampling (minute-(n-q) to before the nth minute); V is compartment acceptor volume (mL); S is volume sampling; and A is the area of membrane (cm^2). The corrected concentration is measured by calculating the levels of active substance using the Wurster equation as follows [18].

$$Q = \frac{CnV + \sum^{n-1}(i-1)\,Ci.S}{A} \quad (1)$$

Fick's law can determine permeability parameters and penetration flux I, where J is flux (mg.sec^{-1}.cm^{-2}); M is the number of active substances transported (mg); S is the area of membrane (cm^2); t is time (sec); P is membrane permeability (cm/sec), and Cd is the number of the active substance (mg).

$$J=\frac{M}{S.t} \quad (2)$$

$$P = \frac{J}{Cd} \quad (3)$$

Validation methods

Limit of Detection (LOD) is the smallest limit test parameter in the sample that can be detected and gives a significantly different response from blanks or noise. Meanwhile, the Limit of Quantitation (LOQ) is the lowest concentration of analyte that can be quantified with accuracy and precision. The LOD and LOQ indicate the sensitivity of the analytical method used and can be determined by the following formula [19], where SD is the standard deviation and b is the slope at the regression curve.

$$\mathrm{LOD} = \frac{3.3\ \mathrm{SD}}{\mathrm{b}} \quad (4)$$

$$\mathrm{LOQ} = \frac{10\ \mathrm{SD}}{\mathrm{b}} \quad (5)$$

Statistical analysis

The data from the physicochemical properties of the patch preparations were analyzed using IBM SPSS Statistics 21 software with a dependent t-test (paired sample t-test). This was performed to determine a significant difference in the patch matrix physicochemical properties test results before and after being treated with temperature variations. Meanwhile, the data obtained from the calibration curve and patch matrix permeation profile were analyzed using the Excel program with a linear regression test.

Results and Discussion

The result of plant determination with No. 069/UN27.9.6.4/Lab/2021 showed that the plant used as study material was Moringa (*Moringa oleifera* Lam.). Plant determination was performed to ensure the plants' correctness.

The yield value of the Moringa leaves ethanolic extract was 8.47% w/w. Also, the organoleptic examination showed a thick extract with a brownish green color and a characteristic odor of Moringa. The test for the moisture content was 0.5%, and this met the specified requirements, which is no more than 10%. The moisture content of more than 10% can affect the quality of the extract because, under these conditions, it is susceptible to microbial and fungal contamination.

The total flavonoid concentration test was performed using the UV-VIS spectrophotometry method. Based on the standard determination of the calibration curve, the regression equation is $y = 0.0032x - 0.0026$ with a correlation coefficient (r) value of 0.9996. According to Miller and Miller [17], these results showed a linear relationship between concentration and absorbance because the correlation coefficient value is more than 0.990; it can be used as a standard curve for further concentration calculations. The total flavonoid concentration in the kelor leaves ethanolic extract was 14.21% w/w, and there is a possibility that this concentration will decrease during the fabrication process of formulating the patch matrix, which is influenced by the temperature factor. The flavonoid total concentration in the Moringa extract is equivalent with the quercetin concentration **(Table 1)**.

Physicochemical stability test

Physicochemical tests were performed before and after the patch was treated with temperature variations for six cycles. The results of organoleptic testing of Moringa leaves ethanolic extract patch revealed a yellowish-brown color. Also, visual observation showed that the patch is smooth and flexible, the extract can be spread homogeneously and has a rough surface texture.

The average value and standard deviation of the patch weights produced before treatment was 1.943±0.160 g, and after treatment was 1.676±0.165 g. This shrinkage of patch weight in this study could be due to a decrease in the moisture content during the treatment of temperature variations for six cycles. Using a paired sample t-test, statistical analysis was conducted to compare the differences in patches before and after temperature treatment. The paired sample t-test showed that the data before and after treatment were significantly different ($p<0.05$), meaning that the temperature difference could affect the weight of the patch. The weight uniformity test aims to determine the uniformity of the resulting patch weight. Moreover, the lighter weight of the patch can increase comfort in its use but does not interfere with activities [9]. The uniformity of the patch weight is related to the active substances contained in the patch matrix [20]. Therefore, the uniformity of weight can affect the therapeutic effect of the preparation.

The paired sample t-test showed that the data before and after treatment were significantly different ($p<0.05$), meaning that the temperature difference could affect the thickness of the patch. The mean value and standard deviation of patch thickness before treatment were 0.733±0.153 mm, and after treatment was 0.65±0.132 mm. This shrinkage of patch thickness in this study was due to a decrease in the moisture content during the temperature variation treatment for six cycles. Patches with uniform thickness are assumed to have consistent weight and active substances contained. Thick patches can make uncomfortable and affect the penetration of the patch's active substances. Meanwhile, too thin patches will make them difficult to use because they tend to be fragile [21].

The pH test aims to determine the safety of the patch preparation as a topical preparation for its application to the skin. Preparations with a pH that is too acidic or alkaline can cause skin irritation. The acceptable pH range for topical preparations is 4.5-6.5. According to the results of the paired sample t-test, the data before and after treatment were significantly different ($p<0.05$), it is mean that the temperature difference could affect the pH of the patch. The pH value of the patch produced before treatment was 6.187±0.146, and after treatment was 5.697±0.087. Although there are significant differences, it meets the pH requirements of topical preparations and is safe to use.

Strong and elastic properties fulfill the requirement of the patch. The resistance of the patch in its application to the skin must show folding endurance to prevent it from easily tearing. Patches that pull easily are assumed to be brittle [22]. The folding resistance test results showed no difference in the patch before and after treatment because it had more than 300 folds. A bast patch has a folding endurance value of more than 300 times [23]. The plasticizer is one of the components in the patch matrix formulation that can affect the elasticity and durability of the patch folds. In this study, polyethylene glycol 400 (PEG 400) was used as the plasticizer. They are essential in transdermal preparations because they guarantee mechanical properties, flexibility, and increased polymer diffusion. A plasticizer is used to form a thin and flexible film from one type of polymer or polymer mixture. Therefore, its use can prevent the film from breaking, tearing, and peeling [24, 25].

Patch that is too moist will reduce the quality of the patch because it can affect the elasticity of the patch and tear easily [14]. The results of the paired sample t-test showed that the data before and after treatment were not significantly different ($p>0.05$). This means that the temperature difference did not affect the moisture content. The resulting value before treatment was 13.987±0.879%, and after treatment was 11.817±2.382%. A low percentage of moisture will produce a relatively stable patch and offer protection from microbial contamination [21]. The hydroscopic properties of the polymer influence the high moisture content value. This is because PEG 400 and propylene glycol are used in the formulation as a plasticizer or film-forming agent. The hydrophilicity properties of polymers, plasticizers, and enhancers can increase the moisture content [21].

Permeation test

In vitro permeation test aims to determine the penetration ability of the drug from the patch matrix in the skin. This test is a crucial parameter in the formulation of the patch matrix because it is related to the therapeutic effect of the preparation. Quercetin is one of the most components in plants representing the flavonol subclass [26]. Previous study reported that the absorption spectrum of flavonols has a wavelength of 350-385 nm in the first

band and 250-280 nm in the second band [27]. In this study, however, the maximum wavelength of total flavonoid obtained from measurements using a UV-VIS spectrophotometer showed two absorption bands at 373 nm and 260 nm. The result of the linear regression equation obtained is y = 0.068x + 0.007 with a coefficient of determination (r^2) of 0.9987 and a correlation coefficient (r) of 0.9993. A linear relationship between concentration and absorbance is indicated by the results because of the value of r > 0.99. Therefore, it can be used as a standard curve for calculating the concentration of active ingredients that penetrate through the membrane. Based on the results of the regression analysis that had been obtained, LOD and LOQ values were determined statistically. The LOD obtained was 0.261 µg/mL and the LOQ value was 0.792 µg/mL.

The permeation test determines the amount of active substance transported through the membrane per unit time interval. Parameters obtained in the permeation test include the cumulative number of active substances transported, flux, and membrane permeability. The cumulative amount is the total number of flavonoids transported across the membrane per unit area of diffusion [18]. According to the Franz diffusion cell principle, the membrane is placed between the donor and receptor compartments. Furthermore, the active substance from the preparation will diffuse across the membrane into a solution in the receptor compartment. The concentration will be measured quantitatively using the UV-VIS spectrophotometry method.

The average value of the cumulative total flavonoid transported through the chicken eggshell membrane for 5 hours was 70.22 g/cm^2, while the average weight transported was 124.29 µg. In addition, the average percentage transported is 31.14% w/w for 5 hours. The test data obtained on the patch matrix of kelor leaves ethanolic extract was similar to the quercetin patch matrix data as a positive control. In the quercetin patch, the total flavonoid transported was 86.08 g/cm^2 with a transported weight of 152.35 µg and a transported percentage of 39.06% w/w for 5 hours. Meanwhile, the patch matrix base was used as a negative control because during formulation, it was only a patch matrix base, hence, it was assumed that there was no flavonoid content **(Figure 1)**.

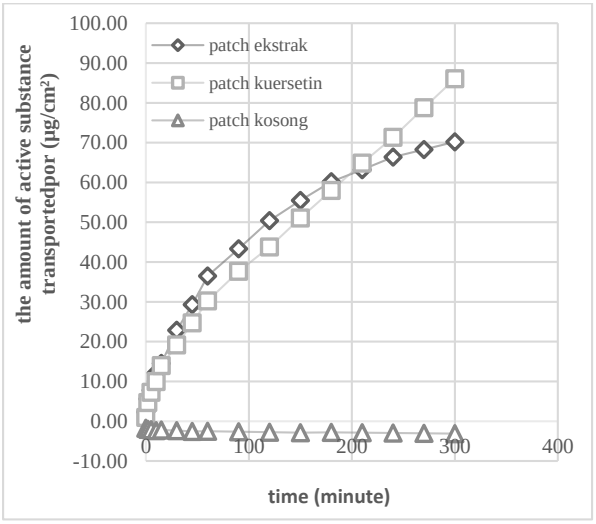

Figure 1. The graphic results of transport through the chicken eggshell membrane of moringa leaves ethanolic extract for 300 minute

This study's result is higher than Ermawati *et al.* [27], which used hydrophilic polymers and extracts as active substances. The total flavonoid transported through the cellophane membrane for 5 hours was 66.57 g/cm^2 with a transported weight of 117.57 µg. However, the results were lower than Saleem and Idris [13], which obtained 53.47% w/w transported for 5 hours through the eggshell membrane. The posibility difference value was because of the essential oil emulsion, chitosan polymer, a natural chitin polysaccharide used [28]. In addition, lactic acid was used as a penetration enhancer to increase penetration in topical preparations [29].

Permeability can be affected by the number of pores, size, and membrane thickness. The membrane permeability can be expressed as a flux or coefficient of permeability. Flux is the amount of drug transported per unit area of the membrane per unit time [30]. The result of flux and permeability membrane of kelor leaves ethanolic extract were $3.90\times10^{-6} \pm 2.18\times10^{-6}$ mg/sec/cm^2 and $2.93\times10^{-6} \pm 1.69\times10^{-6}$ cm/sec. In this study, the results obtained were not much different from previous studies using cellophane membranes, namely flux of 3.7×10^{-6} mg/sec/cm^2 and membrane permeability of 3.29×10^{-6} cm/sec [27]. This difference in value is possible due to differences in the membrane structure used. The specifications of the cellophane membrane used in the previous study had an MWCO of 6-8000 Da. Meanwhile, the pore size of the eggshell membrane is 8.78 µm ± 2.6 µm [31, 32].

Table 1. The patch formula of Moringa leaves ethanolic extract, where the patch base and quercetin patch as a comparative patch

Ingredients	Weight (g)			Functions
	Patch base	Moringa patch	Quercetine patch	
Extract	-	0.30	0.043	Active component
Polyvinyl alcohol	0.20	0.20	0.20	Polymer
Alpha-cellulose	0.40	0.40	0.40	Polymer
Poliethylene glycol 400	0.60	0.60	0.60	Plastisizer
Propylene glycol	0.60	0.60	0.60	Penetration enhancer
Phenoxyethanol	0.04	0.04	0.04	Preservative

Ethanol 70%	1.00	1.00	1.00	Solvent
Water	6.50	6.50	6.50	Solvent

Table 2. The physicochemical properties test of moringa leaves ethanolic extract patch, before and after temperature treatment

Physicochemical properties	Before temperature treatment	After temperature treatment
Weight	1.94±0.16 g	1.68±0.17 g
Thickness	0.73±0.15 cm	0.65±0.13 cm
pH	6.19±0.15	5.70±0.09
Folding endurance	>300 times	>300 times
Moisture content	13.99±0.88 %	11.82±2.38 %

Conclusion

The Moringa leaves patch matrix formula with a polymer combination of PVA and alpha-cellulose (1:2) was able to penetrate chicken eggshells membranes with a speed of 3.90×10^{-6} $mg.sec^{-1}$ $.cm^{-2}$ and membrane permeability of 2.93×10^{-6} cm/sec. Furthermore, the total transported flavonoid weight was 124.29 µg, and the percentage of penetration obtained was 31.14%w/w. Temperature variations significantly affect the physicochemical properties of the patch matrix of kelor leaves ethanolic extract, such as thickness, pH, and weight uniformity. However, it does not affect the patch's folding endurance and moisture content. The results showed that the Moringa patch can be developed as a topical anti-inflammatory agent.

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Ethics statement: None

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